

The Essentials of
Human Embryology

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Third Edition

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PREFACE TO THE THIRD EDITION

The present revision is the most extensive since the book was first published. The plan and ideals of the earlier editions have been retained. The primary object of the revision has been to incorporate those recent advances in embryological knowledge which properly come within the scope of such a book. Inasmuch as this book is designed to furnish a concise presentation of human development, its size has not been increased, despite a constant urge to make more elaborate use of the important new embryological information which in recent years has been produced in great abundance.

The chapter on early development is wholly new. It is a direct account of human development, based upon the increasingly adequate human material and supplemented by the recent excellent work on the monkey, *Macacus rhesus*. Other sections which have been extensively rewritten are those dealing with the fetal membranes, the early mesoderm, the organs of respiration, the body cavities, the blood vascular system, the lymphatics, the reproductive organs, and the organs of special sense. New illustrations have been substituted at appropriate places, and corrections have been made in other figures.

The writer is grateful to the many authors whose publications have furnished information upon recent progress in embryology. He would also express his continued indebtedness to many less recent authors whose works have become classics, and to which the writer of a textbook must constantly refer if he is to maintain perspective in the interpretation of more recent publications. In the treatment of obscure points on which investigators have not yet come to agreement, the writer has made every effort to arrive at a fair evaluation of the evidence, although doubtless his own personal bias also enters into his presentation. As in the earlier editions, no attempt has been made to quote or to catalog individual authors, a procedure which the scope of the book hardly permits, except inasmuch as credit for illustrations indicates certain important sources of information.

G S D

PREFACE TO THE FIRST EDITION

This textbook of human embryology has been written primarily for medical students and secondarily for those who are preparing for the study of medicine in schools where embryology is a prerequisite subject. It presupposes a knowledge of the gross and microscopic structure of the human body and is designed especially to interpret and clarify such knowledge. It may also be used with good results by students who have a knowledge of mammalian anatomy such as may be gained from a course in comparative anatomy, if dissection of a mammal is included. It is written for students who have had no previous training in embryology but who wish a knowledge of human development and of embryological principles as a part of their training in human anatomy and as a foundation for obstetrics.

The book is frankly a human rather than a comparative embryology. Accordingly, the primary treatment throughout deals with human development, with reference to other forms only where necessary to fill gaps or to introduce comparisons of evident interest to persons who are not specialists in the subject of embryology. The author has tried to include those facts about human development which are most useful in rounding out a knowledge of adult human structure, and in giving an understanding of the relation between the mother and the unborn child. It has been the aim throughout to present the embryo not merely as a human being in the making, but also as a living individual with all the life activities of other living beings.

The author has tried to make the book as brief as is consistent with an adequate presentation of the subject. Accordingly, many details have been omitted, and the treatment at places is almost diagrammatic in its nature. The brevity of treatment is a recognition of the fact that embryology is only one of the many subjects which a medical student ought to master, and, furthermore, that it is one to which he cannot devote a great deal of time. It has a true textbook to serve as a basis for recitations, discussions, and supplementary lectures rather than as a reference book to supplement a lecture course.

The importance of illustrations as an indispensable aid in visualizing the process of development has been definitely recognized. It has not, however, been the plan to include an excessive number of figures, but rather to use a carefully selected and executed series, all of which contribute directly to the story of development, as told in the printed pages of the book. Most of the figures are simple, many of them diagrammatic. Many of them are original; others have been chosen from periodical literature of recent years; others are excellent illustrations by various earlier investigators, which have been familiar figures in textbooks for a generation.

The original figures are not intended to be contributions to embryological knowledge, but are rather designed to express well-known facts in terms readily understandable by beginners in the subject. The figures from other sources have nearly all been redrawn and relabeled in full, in order to secure uniformity of style and terminology. Credit for all illustrations is given in the legends. To all who have thus contributed illustrations, the author wishes to express his indebtedness, with the hope that through new grouping and manner of presentation these figures may continue to fill a useful place in the teaching of embryology.

For the general ideals and manner of working out the details, both of manuscript and figures, the author is, of course, indebted to many persons who have had either direct or remote influence. The greatest single influence has been the students in his classes, who have constantly had difficulty in grasping the facts concerning human development. The manner of presentation employed follows the plan which has been found effective in presenting the subject to classes. During the preparation of the book, both manuscript and figures have been used in teaching, and in this way points of weakness and strength have been made apparent. A goodly number of the illustrations have been used as blackboard drawings, chart figures, and lantern slides, through several years.

A course in human embryology should include adequate laboratory work upon embryos of chick, pig, etc., together with the study of such human material as may be available. No laboratory directions are, however, included in the present volume, because so many teachers prefer to prepare their own laboratory instructions.

G. S. D.

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CHAPTER I

THE GENERAL PRINCIPLES OF DEVELOPMENT

A. THE MEANING OF EMBRYOLOGY

Embryology is the study of development. Development, in the broad sense, embraces all changes in the individual from the beginning of life until the attainment of complete adult structure. More commonly, however, the treatment of the subject is restricted to include only that part of the developmental process which takes place before the hatching of the egg or the birth of the young individual. This restricted use of the term is, in a very significant sense, justified by the fact that the most pronounced part of development, though by no means all of it, takes place during this early period. Moreover this is the part of development that is wholly concealed from the ordinary observer, because it takes place within the egg or the body of the mother, so that special means must be employed for its study. It is also of great significance that the unborn individual lives under wholly different conditions from those which will surround it after birth. Birth, therefore, marks the beginning of a new mode of existence rather than the completion of development or even an important milestone in its progress.

B THE IMPORTANCE OF EMBRYOLOGY

For all persons, some knowledge of prenatal life is of definite value, but to the medical student, who expects to deal with human life in its most intimate phases, such knowledge is essential. To understand human beings, one must know life from the beginning to the end. Embryology is a part of anatomy — gross and microscopic, normal and abnormal. A knowledge of embryology is essential as a foundation for obstetrics. The relation between these two subjects takes on significance when we remember that a large part of the work of the physician consists of caring for the unborn infant and the woman who bears him, and of bringing these two persons safely through the critical period of birth.

C THE NATURE OF REPRODUCTION

If one is to understand development, he must first have a knowledge of the process of reproduction by which development is initiated

Because of the reader's training in zoology, this subject need only be reviewed briefly.

It will be remembered that reproduction consists essentially in the separation of a part of the parent to form a new individual. This separation is sometimes accomplished by an asexual process, such as the fission of protozoa or the budding of hydra, but more frequently by the sexual method, involving two parents. Each parent contributes a single cell, the female giving the ovum or egg, the male the spermatozoon or sperm. These two cells unite in a process known as fertilization to form one cell, the fertilized egg. This fertilized egg is the beginning of a new individual.

It will be further remembered that in aquatic animals the eggs and sperms are shed into the water, where fertilization occurs and development goes on, usually without a semblance of parental care. In land animals, however, the sperms are introduced directly into the reproductive tract of the female, where fertilization takes place. After fertilization the eggs may either be discharged and develop outside the mother, as in birds, or they may be retained, so that they undergo their development within her body, as among the mammals. The latter is the most advanced form of reproduction and insures the best developmental conditions for the young, though it also involves greater burdens and hazards to the mother. This method requires highly specialized organs for the protection and nourishment of the unborn young, as well as for the expulsion of the young at the proper time.

D. THE NATURE OF DEVELOPMENT

Historical Theories. Before the perfection of modern microscopic methods, theories concerning development were based largely upon speculation. Two views contended for mastery. The advocates of preformation believed that the "germ" contained a miniature individual with all the parts of the adult. Some maintained that this individual existed in the sperm and found proper nutritive conditions in the egg, whereas others insisted that it resided in the egg and that the male element merely stimulated it to growth. The advocates of epigenesis, on the other hand, believed that the body and its parts arose from formless substance by a process of gradual organization. The true nature of development was not understood until the investigations stimulated by the cell theory of Schleiden and Schwann (1839) showed the egg and sperm to be cells. O. Hertwig (1875) was the first to observe and understand the process of fertilization and thus to demonstrate clearly the nature of the contribution made by each parent.

The Modern View All students of microscopic anatomy are now well aware that the human body is composed of structural units known as cells and will be readily able to appreciate the nature of development, which begins with the single cell formed by the union of the egg and sperm. Four main processes are involved in embryonic development

1 Cell Multiplication By repeated divisions the single cell gives rise to the millions of cells composing the adult body, all of which are lineal descendants of the original fertilized egg

2 Cell Differentiation or Specialization Cell specialization is the process by which these many cells develop along different lines, giving rise to the various kinds of cells which form the several tissues of the adult

3 Organ Formation During the process of development the tissues become arranged in definite relations to produce the organs and the characteristic form of the body. These three phases of development are going on at the same time, though, of course, cell multiplication must progress to a certain point before specialization can take place

4 Growth The fertilized ovum has a volume of about 0.0014 cu mm. During development a great increase in size is brought about by the assimilation of foods, so that by the time of birth the developing human being is about two and one-fourth billion times as large as the fertilized egg. By the time adult size has been attained, the individual has, on the average, increased in size about twentyfold more, so that the adult is about forty-five billion times as large as the fertilized egg with which it began its individual existence

E THE STRUCTURE OF THE CELL

In order to understand clearly the process of development, one must understand the structure of the cell in rest and division

The Resting Cell

A typical cell has the following parts (1) **The cytoplasm** The cytoplasm forms the greater part of the cell. It is a mass of protoplasm with a more or less well developed cell membrane at its surface. (2) **The nucleus** The nucleus is a more specialized mass of protoplasm within the cytoplasm, bounded by the nuclear membrane. Within it are numerous chromatin granules suspended by a very delicate network of linin threads, the spaces of which are occupied by a semifluid mass, the nuclear sap. There is usually present also the nucleolus, a body of variable structure. (3) **The centrosome** In the cytoplasm near the nucleus there is in most cells a very minute body, the centro-

some, which is easily overlooked in the resting cell but is more conspicuous during cell division.

Figure 1A illustrates the above-named parts of the cell. Within both nucleus and cytoplasm there are other structural elements yet more

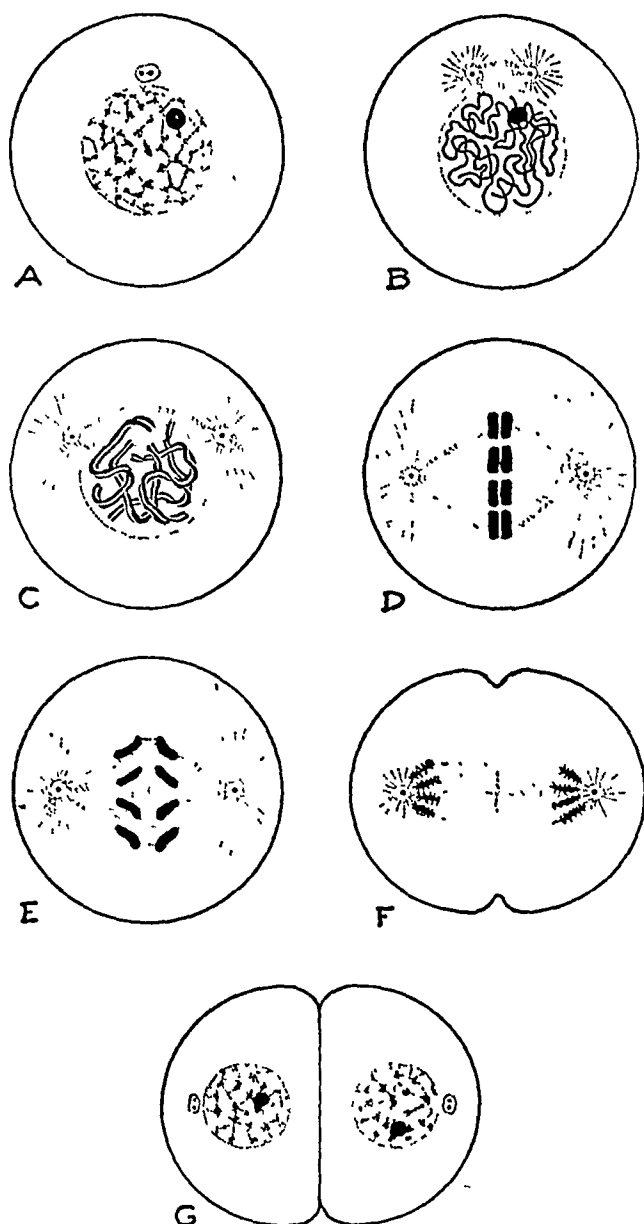


FIG. 1. Diagrams showing mitosis. The cells represented have four chromosomes. A, resting stage. B, C, prophase D, metaphase. E, anaphase. F, telophase. G, daughter cells.

minute which are not shown in this figure. From this brief account it will be evident that the cell, though very small, has a definite organization which attains considerable complexity.

Cell Division

It is now well known that all cells arise by the division of other cells, the division usually accomplished by a process known as mitosis. The following steps in the process are commonly recognized, though the division into stages is merely a matter of convenience, the process being a continuous one (Fig 1)

1 Prophase or preparation for division The granules of chromatin become united into a long, continuous thread, the spireme, which is slender at first but soon grows thicker. This thread then breaks into a number of segments, the chromosomes. Meanwhile the nuclear membrane and the nucleolus disappear. About the same time, the centrosome divides into two (if division has not previously occurred), and the astral rays appear, radiating from each centrosome. The two centrosomes with their asters gradually migrate toward opposite sides of the cell but remain connected by the delicate spindle fibers. The chromosomes now take their place in the equatorial plane midway between the two centrosomes.

2 Metaphase Each chromosome splits into two similar and equal chromosomes, thus forming two similar groups of daughter chromosomes. This splitting may take place before the chromosomes reach the equatorial plane, in some cells as early as the spireme stage.

3 Anaphase These two groups of chromosomes separate and migrate toward opposite centrosomes.

4 Telophase The chromosomes now return to the diffuse granular form characteristic of the resting nucleus, and the other nuclear structures of the resting stage appear, producing two daughter nuclei from the material of the one parent nucleus. After the division of the nucleus, the cytoplasm becomes separated into two masses by a constriction midway between the two nuclei, thus completing the division of the cell.

Points of Interest

Certain points in the process of division are worthy of further comment. (1) The number of chromosomes in the cells of a given species is always the same and is characteristic of that species but different from the number in other species. (2) Chromosomes differ in form and size, ranging from small spherical masses to long rods which are often bent to resemble the letter V or J. (3) Within one cell are often found chromosomes of different sizes and shapes, occurring nearly always as pairs of similar chromosomes. The forms for each species are definite and characteristic, differing from those of other species. (4) There is

good evidence that chromosomes maintain their identity through successive cell generations, though during the resting stage they are indistinguishable to the observer. This means that chromosomes arise by the division of pre-existing chromosomes. (5) There is much evidence that chromosomes are the structures that are responsible for the transmission of hereditary characteristics from parent to child and are largely instrumental in directing the course of embryonic development. (6) In this connection it is of interest to emphasize the elaborate care which is exercised to insure an equal division of the chromosomes at each division of the cell. (7) As will be pointed out in greater detail at a later time, it has been observed in many different species of animals that there is a sexual difference in the chromosomes, those of the two sexes being slightly unlike and usually different in number.

The alternating periods of division and rest constitute what may be called the reproductive cycle of cells. It must be remembered that the so-called rest period is, in an important sense, not one of rest at all but one of great metabolic activity, the time during which the two daughter cells grow in size, usually until they have become as large as the mother cell. It is by the growth of the individual cells that the size of the embryo or young animal increases.

The time occupied in the process of mitosis is short in relation to the length of the resting stage. In young embryos of certain animals, for example, where the time between the periods of division is about one hour, the time occupied by the process of mitosis is only five or ten minutes. Even in young embryos, when division is rapid, most of the cells which we see during microscopic examination are in the resting period. It is only occasionally that one appears in division, except in especially favorable material where division is unusually rapid.

CHAPTER II

THE GERM CELLS

Among the many types of specialized cells in the human body, such as muscle, nerve, and bone, there is only one kind which has the capability of producing a new individual. These cells are known as germ cells, in contrast to the others, which are called somatic cells.

The germ cells are located in the gonads (the ovary and the testis). They are cells held in reserve within these organs, from them at appropriate intervals the eggs and sperms are produced. They are in one sense specialized cells, in that they are set apart expressly for the purpose of reproduction and do not take part in other specialized activities of the body. In another sense they are wholly unspecialized, in that they have within them

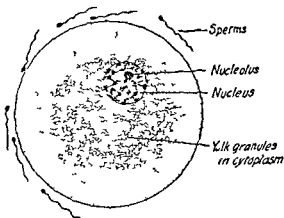


FIG 2 Outline drawing of the mature human ovum with several sperms drawn to the same scale

the possibility of producing all kinds of cells of the body, whereas the cells of other tissues, in becoming specialized for their particular work, have to a very great extent lost the capability of giving rise to anything else. Somatic cells are concerned with the activities of the body in which they exist, the germ cells are concerned with the generations to come.

The Sperm The human spermatozoon or *sperm* is a very small, highly specialized cell with the power of motility. It has a head containing the condensed nucleus surrounded by a very little cytoplasm, a small middle section containing the centrosome, and a slender tail composed of cytoplasmic material. The whole sperm has a length of about 55 microns (0.055 mm), about one-tenth of which is included in the head (Fig 2). The details of the structure of sperms are described in textbooks of histology and need not be repeated here.

The Egg The mature human ovum or *egg* is a spherical cell of the

ordinary type, in the cytoplasm of which is a small amount of yolk material in the form of fine granules (Fig. 2). It has a diameter of about 140 microns (0.14 mm.) or less, but is many thousand times greater in volume than the sperm; nevertheless the two have equal potentialities as far as inheritance is concerned.

A. GENERAL ACCOUNT OF MATURATION AND FERTILIZATION

The process by which the reserve germ cells in the gonads become eggs and sperms is known as maturation. The process is fundamentally the same in the two sexes but differs in certain details. The following description of maturation and fertilization is not based upon any special animal, but is rather a generalized, diagrammatic statement designed to present the essential facts in a simple form.

Maturation of the Sperm (Spermatogenesis). Sperms arise in the tubules of the testis by multiplication of cells which are known as **spermatogonia**. The spermatogonia multiply by mitosis with sufficient frequency to maintain a reserve of cells, which are drawn upon in the process of spermatogenesis. In this process certain of the spermatogonia become **primary spermatocytes**. Spermatogenesis involves three generations of cells and two cell divisions. Each first spermatocyte divides in the **first maturation division** to produce two **second spermatocytes**. Each second spermatocyte quickly undergoes the **second maturation division** to produce two **spermatids**. Each spermatid which is a cell of the ordinary form undergoes a **metamorphosis** which changes it into a **sperm**. Thus, as the result of the two maturation divisions four sperms come from each primary spermatocyte (Fig. 3).

The two maturation divisions differ from ordinary mitotic divisions in that *whereas the cells divide twice, the chromosomes divide but once*, the result being a reduction in the number of chromosomes in each of the spermatids to one-half the number in the primary spermatocyte.

The behavior of the chromosomes during the maturation divisions is shown in a very diagrammatic manner in Fig. 3, which represents an instance where the number of chromosomes is eight. Of these eight chromosomes, the six shown in black are known as **autosomes**. They occur in pairs, the members of a pair being similar in size and shape. The other pair, known as the **X** and **Y** chromosomes, are unequal in size. If the X and Y chromosomes are ignored for the present, the course of maturation is as follows.

In preparation for the first maturation division, the first spermatocyte increases decidedly in size (the growth period), after which the

chromosomes unite temporarily in pairs, similar chromosomes coming together. This pairing is known as synapsis. While joined in the synaptic union, each chromosome divides into two, thus making of each

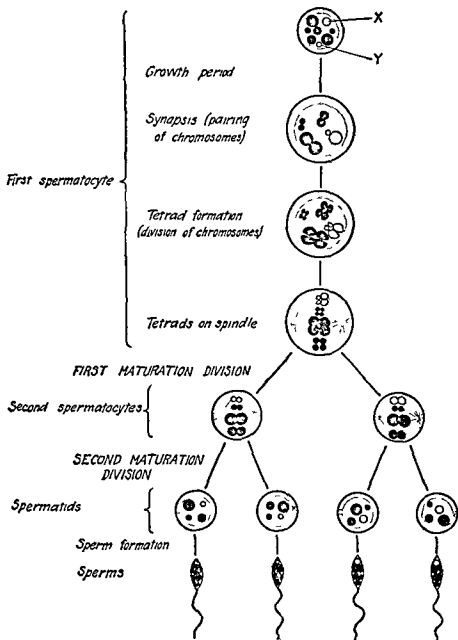


FIG 3 Diagrams showing the maturation of the sperm as it occurs in cells having three pairs of autosomes and the XY pair

pair a group of four, known as a tetrad. Thus the number of tetrads is just one-half the number of chromosomes originally present, but the actual number of chromosomes has been doubled.

In the first maturation division, which now follows, each tetrad separates into two dyads, each composed of two chromosomes. In the second maturation division, which follows immediately, the chromosomes do not divide, but the dyads of the second spermatocytes separate into the individual chromosomes, giving each of the spermatids just half the number of chromosomes present in the first spermatocyte.

Maturation of the Egg (Oögenesis). The primitive ova found in the cortex of the human ovary are in a stage corresponding to the first spermatocyte and are accordingly known as first oöcytes. They are much smaller than the mature egg will be, but just before maturation takes place they grow rapidly. Maturation of the egg should not be confused with ovulation, the discharge of the egg from the ovary. Maturation takes place about the same time as ovulation, possibly being completed just before it in the human ovum.

The maturation of the egg, like that of the sperm, is accomplished by two maturation divisions, but with the difference that, though the nucleus divides equally, the cytoplasm divides very unequally. The cytoplasm of the first oöcyte divides unequally at the first maturation division, producing a large cell, the second oöcyte, and a minute one, the first polar body (Fig. 4). The second oöcyte, by the second maturation division, which is likewise unequal, gives rise to the mature egg and the second polar body (Fig. 4). The large cell or mature egg is now ready for fertilization.

The polar bodies, though receiving very little cytoplasm, receive three-fourths of the nuclear material and thus correspond to three of the four spermatids. If one imagines the first polar body dividing at the second maturation division as it does in a few species of animals, the parallel to the maturation of the sperm is more evident (Fig. 4). The polar bodies are much smaller in proportion to the egg than they are shown in this figure. They soon degenerate.

Though the cytoplasm divides very unequally in the two maturation divisions of the egg, the nuclear divisions are just the same as in the sperm. In the first division synapsis and tetrad formation occur, and the second oöcyte and the first polar body receive equal numbers of dyads (Fig. 4). In the second division the dyads separate into individual chromosomes. Thus the ripe egg and the second polar body each receive just half as many chromosomes as were originally present in the first oöcyte.

Fertilization. Fertilization is the process of union of one egg and one sperm. It has been studied in many species of animals, chiefly aquatic forms, where it takes place in the water and may easily be watched under the microscope. Though many sperms may surround the ripe

egg, only one is involved in fertilization, for the entrance of one sperm into an egg causes a change in the surface of the egg which prevents the entrance of others

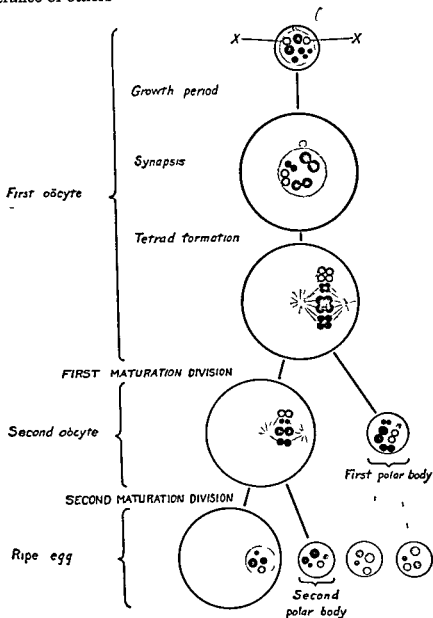


FIG 4 Diagrams showing the maturation of the egg as it occurs in cells having three pairs of autosomes and the XX pair

After the completion of maturation, the nucleus of the egg, with the reduced number of chromosomes, takes the form of an ordinary resting nucleus, and the individual chromosomes can no longer be distinguished. It is now known as the female pronucleus (Fig 5A). The sperm head, containing the condensed nucleus of the male germ cell, is very small when it enters the egg, but it soon expands into a

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The First Division of the Fertilized Egg The fertilized egg immediately begins the process of development, the first phase of which is cell division. These divisions are mitotic divisions of the ordinary sort described in Chapter I. In preparation for the first division, the chromosomes of the two pronuclei again assume the form of definite, compact, chromatin masses (Fig 5D). When the nuclear membranes disappear, the two groups of chromosomes mingle in the equatorial plate, thus restoring the original number by the mingling in one nuclear group of the reduced numbers found in the two pronuclei (Fig 5E).

Each of these chromosomes now divides in the manner characteristic of ordinary mitotic divisions, and the two groups of daughter chromosomes migrate toward the two poles (Fig 5F), the result being that each of the two daughter nuclei receives one-half of each chromosome contributed by the two parents in the egg and the sperm. After the completion of this division the two nuclei again assume the resting form, in which the individual chromosomes become indistinguishable. In the continued development of the egg these two cells, after a period of growth, divide again. In this second division each of the chromosomes again divides, and each of the four resulting cells receives a portion of each of the chromosomes brought in by the egg and the sperm. Similarly, in each of the many following divisions, each chromosome divides into two equal chromosomes, which, during the resting stage, grow in size only to undergo division at the next mitosis.

Because of the continuation of the alternate growth and division of chromosomes, each cell of the body at any time during development has the original number of chromosomes, moreover these chromosomes are the direct descendants of the chromosomes contained in the egg and sperm, one-half of them from each parent.

Fertilization and Sex Determination It has been observed in many species of animals that in addition to the characteristic number of autosomes, those chromosomes which occur in equal pairs and are alike in both sexes, other chromosomes, which differ in the two sexes and which are commonly called **accessory chromosomes**, are also present. The difference between male and female animals extends, therefore, to visible characteristics of the nuclei of the cells.

A common condition is that illustrated in Figs 3 and 4, in which the accessory chromosomes of the male are a pair of unequal size, the large one known as the **X chromosome** and the small one as the **Y chromosome** (Fig 3). The cells of the female differ from those of the male in that they contain two accessory chromosomes of equal size known as **X chromosomes** (Fig 4).

nucleus of the ordinary type, the male pronucleus (Fig. 5*B* and *C*). The male and female pronuclei, about equal in size, commonly lie side

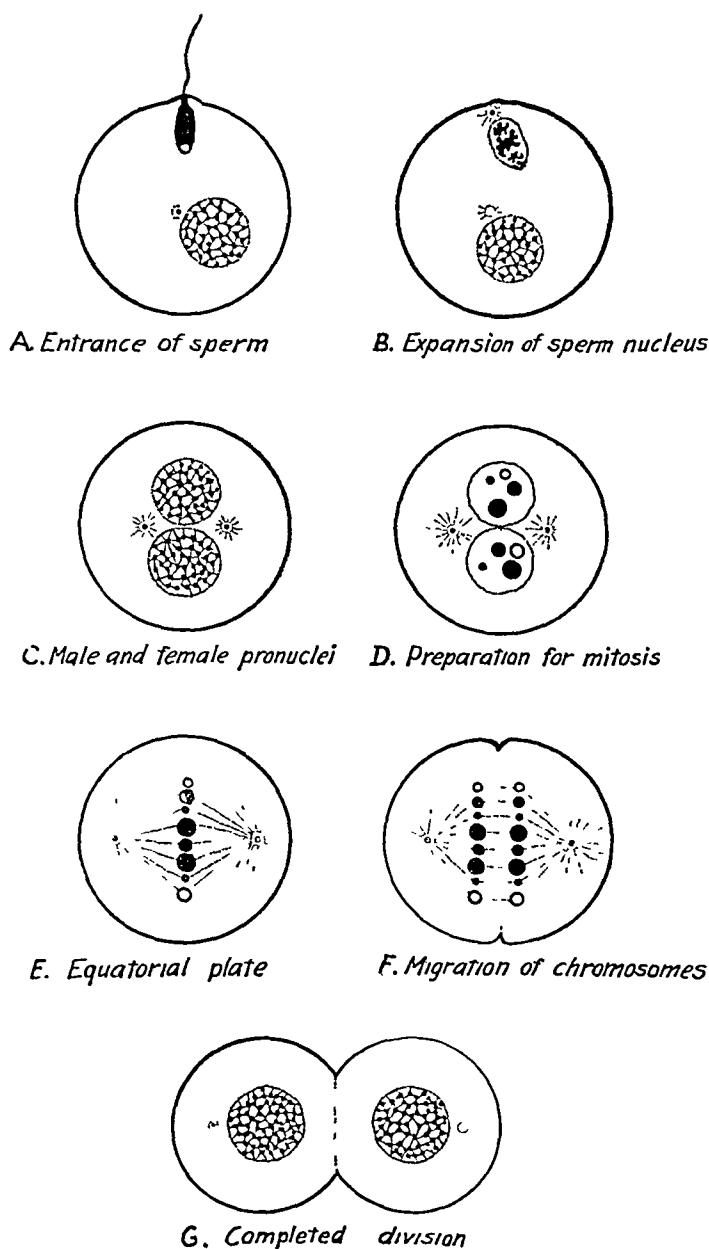


FIG. 5. Diagrams showing the process of fertilization and the first cleavage of the fertilized egg. The ripe egg contains three autosomes and one X chromosome; the sperm shown has three autosomes and the Y chromosome, which gives rise to the male condition (XY) in the fertilized egg. A sperm containing an X chromosome (not shown in this figure) would produce the female condition (XX).

by side and do not mingle to form a single nucleus until the first division of the fertilized egg.

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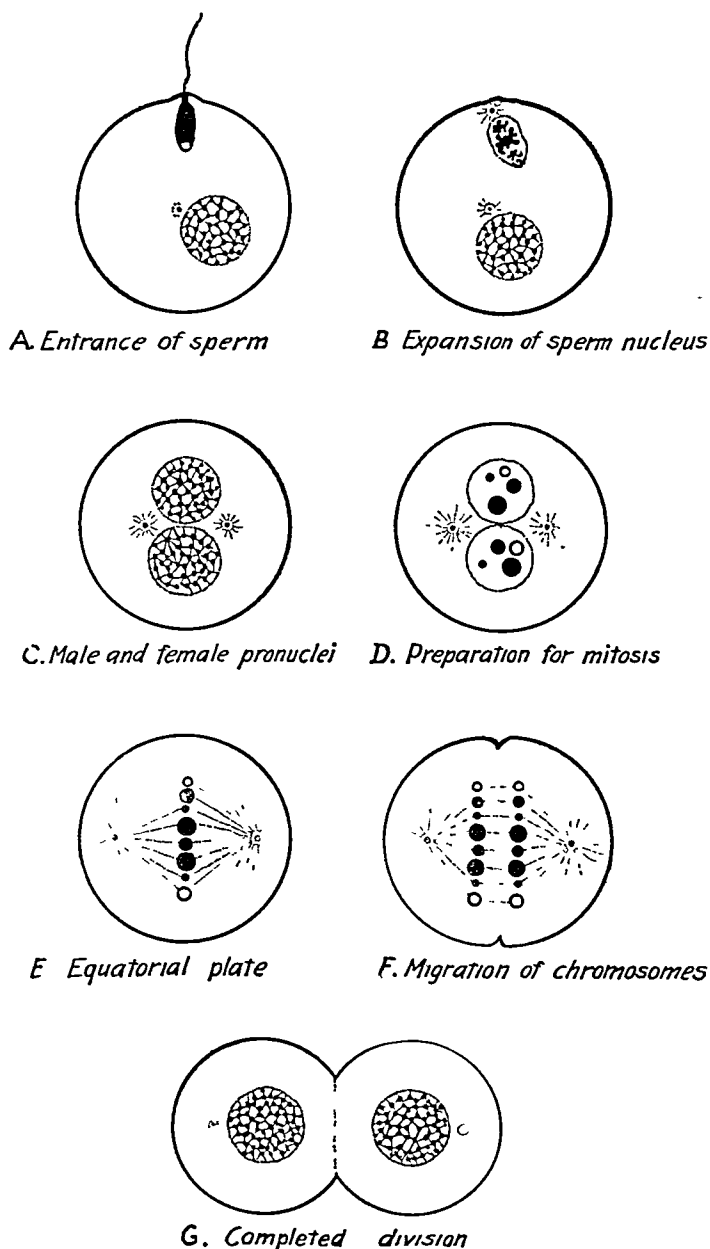


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time been advocated, most of them with little or no support from observed facts. It is safe to say that at the present time the great majority of biologists accept the view just outlined, that sex is in all probability determined at the time of fertilization. The part played by other factors in the full development of sexuality will be discussed in Chapter XVII.

B SPECIFIC EXAMPLES OF MATURATION AND FERTILIZATION

1 The Opossum

To illustrate more fully the behavior of the chromosomes during maturation and fertilization, let us consider the opossum as described by Painter (1922). The process of maturation has been studied in many species of animals belonging to several different Phyla, any of which might be used as an illustration, the opossum is chosen because it has been carefully studied and is close to the human condition.

Somatic Cells In the somatic cells of the adult opossum, it is impossible to count the number of chromosomes, but in the embryo Painter could count them. In a number of embryos old enough so that the sex could be determined by external examination, he found that all the opossum embryos have twenty-two chromosomes. In both sexes, twenty of these chromosomes, the autosomes, occur in pairs. In the male the accessory chromosomes are a pair of very unequal size, the X being much larger than the Y chromosome (Fig 6A). In the female the accessory chromosomes consist of two X chromosomes of similar size and shape (Fig 6B).

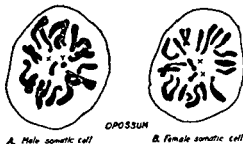


FIG 6 Dividing somatic cells of opossum embryos. A, cell from male embryo showing 20 autosomes and the XY pair. B, cell from female embryo, showing 20 autosomes and the XX pair (Redrawn from Painter, in *Jour Exp Zool*, Vol 35)

Maturation of the Sperm In the spermatogenesis of the opossum it was found that the spermatogonia in their divisions have, like the somatic cells of the male embryos, twenty autosomes and XY (Fig 7A). In the first spermatocyte these twenty-two chromosomes unite in synapsis to form eleven pairs, which divide to form eleven tetrads. The X and Y chromosomes act as a pair, making one unequal tetrad. In the first maturation division the tetrads separate, the X and Y chromosomes going into different cells (Fig 7B). Thus one of the second spermatocytes gets two X chromosomes and the other two Y

In the maturation of the sperm, the accessory chromosomes behave as do any of the pairs of autosomes, uniting with each other in synapsis. This pair forms a tetrad of two large and two small chromosomes. These separate into dyads and the dyads into individual chromosomes. The result is the formation of two kinds of sperms in equal numbers, one of which contains the X and the other the Y chromosome (Fig. 3).

In the maturation of the egg, the two X chromosomes act as a pair, undergoing synapsis, tetrad formation, and the other stages shown in Fig. 4. In the first maturation division, the second oöcyte and the first polar body each receive a dyad (two X chromosomes). In the second division, the ripe egg and the second polar body each receive one X chromosome (Fig. 4). In this respect all the ripe eggs are alike, not of two kinds as are the spermatozoa.

If the egg is fertilized by a sperm containing a Y chromosome, the XY condition is produced, which is known to characterize the cells of male individuals (Fig. 5); but if by a sperm containing the X chromosome, the XX condition of the female results. The sex of the new individual is thus determined at the time of fertilization, the production of a male or a female depending upon which of the two types of sperms enters the egg.

The type of accessory chromosomes described above, though found in many animals, is not the most common type. In the majority of species which have been studied, it has been found that, although the female condition is just as described, two X chromosomes being present, only one accessory chromosome, the X chromosome, is present in the male. The cells of the male have, accordingly, one less chromosome than occurs in the female. The condition of this type of male cells may be imagined by omitting the Y chromosome from Fig. 3. In such species the female-producing sperms have an X chromosome, whereas the male-producing sperms have none.

The account of maturation and fertilization presented in the preceding paragraphs may be applied to a wide range of animals by substituting for the three pairs of autosomes the particular number which characterizes each species and by using the proper type of accessory chromosomes. It is also of interest to note that in the birds and the Lepidoptera the sexual relation of the accessory chromosomes is just the reverse of that observed in other animals, so that, although all the sperms are of the same type, there are two kinds of eggs, one of which gives rise to males and the other to females.

This view of sex determination is of special interest when it is remembered that many methods of sex determination have from time to

Maturation of the Egg The details of the maturation of the egg have not been observed in the opossum, but from observations upon other animals the accuracy of the following account may, with considerable confidence, be assumed. The first oocyte, in all probability, has twenty autosomes and two X chromosomes, because this is the condition found in female embryos (Fig 6B). The steps in the process are probably as follows

Oogenesis in the Opossum

Female somatic number

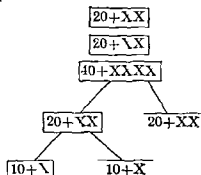
First oocyte { before tetrad formation
after tetrad formation

First maturation division

Second oocyte and first polar body

Second maturation division

Ripe egg and second polar body



The result of this process is that all the ripe eggs are alike, each receiving ten autosomes and one X chromosome

Fertilization and Sex Determination Inasmuch as all the mature eggs carry the X chromosome, and the sperms are of two kinds, half carrying the X and half the Y chromosome, there is the possibility of two kinds of fertilized eggs — one with the XY in addition to the autosomes and the other with the XX and the autosomes, the two possibilities being expressed as follows

Fertilization of the Opossum Egg

Mature Egg		Sperm		Fertilized Egg
$10+X$	with	$10+X$	gives	$20+XX$ (female)
$10+X$	with	$10+Y$	gives	$20+XY$ (male)

These two chromosome complexes are exactly those which Painter found in the opossum embryos of the two sexes

2 The Human Species

Human chromosomes during spermatogenesis have received much study but without full agreement of results. Careful workers agree that in the male there are forty-six autosomes, but whereas some describe both X and Y chromosomes, making forty-eight in all, others are unable to find a Y chromosome, making a total of only forty-seven

chromosomes. In the second maturation division two types of cells are apparent, one of which shows an X chromosome going into each spermatid and the other a Y for each (Fig. 7C and D). Thus two of the four spermatozoa formed from the first spermatocyte receive the

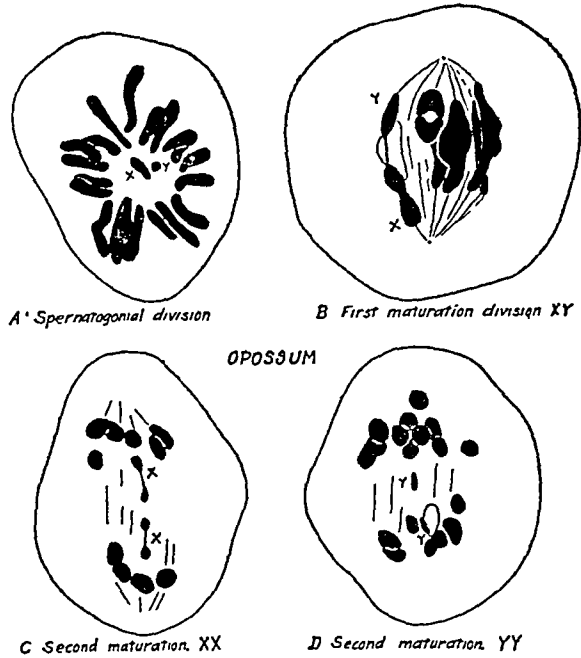
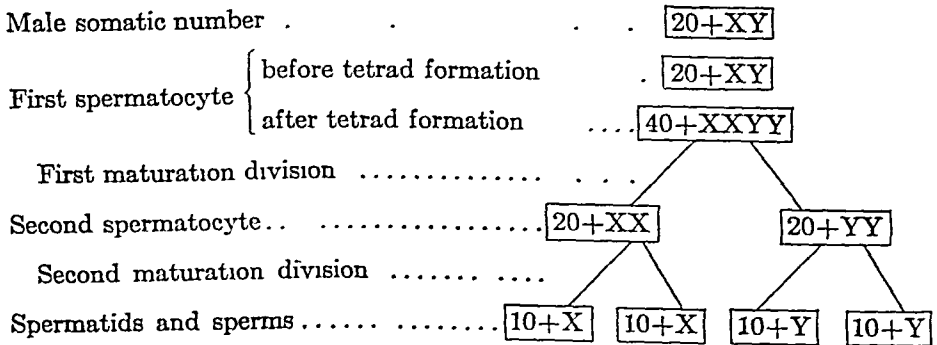


FIG. 7. Maturation of the opossum sperm. A dividing spermatogonium, showing 20 autosomes and the XY pair. B, first maturation division, showing the X chromosome going to one pole and the Y to the other. Not all the autosomes are shown. C, second maturation division, showing the spermatocyte which received the X chromosome at the first maturation division. D, second maturation division, showing the spermatocyte which received the Y chromosome. (Redrawn from Painter, in *Jour. Exp. Zool.*, Vol. 35.)

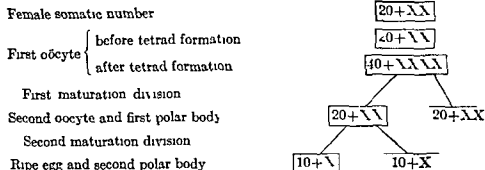
X chromosome in addition to ten autosomes, and two the Y in addition to ten autosomes. A diagrammatic description of these events follows.

Spermatogenesis in the Opossum



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Oogenesis in the Opossum



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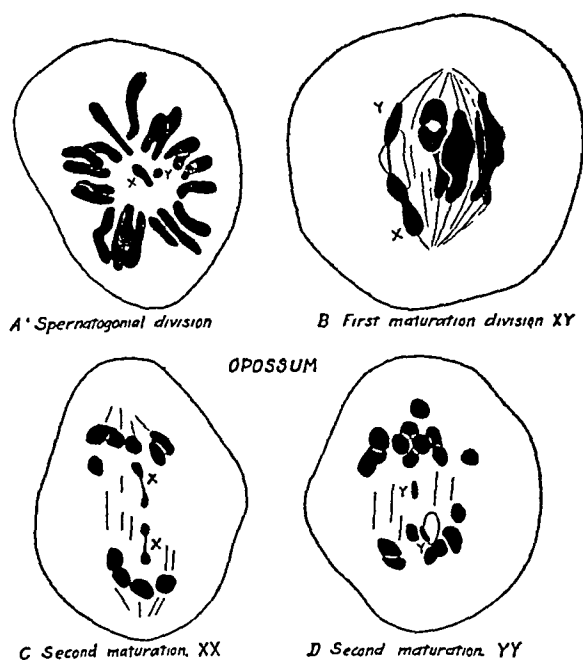
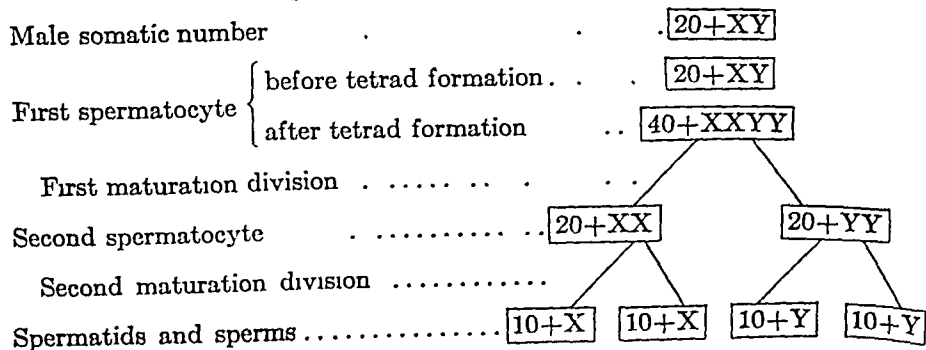


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Spermatogenesis in the Opossum



previously indicated, the chromosomes seem to be the bearers of hereditary characteristics. Available evidence indicates that very probably they are responsible for the transmission from generation to generation of not only the stable characteristics which are common to all members of the species, but also the variability of structure and function which produces family traits and individual peculiarities. The successful accomplishment of the complex events of embryonic development in all probability depends upon the existence of a proper chromosome structure in the fertilized egg. The entire architecture of the adult body is accordingly, largely at least, predetermined by the composition of the chromosomes in the egg and sperm.

Experimental evidence indicates that each chromosome is responsible for the development not of one character, but of a group of several characters, the development of the characters being due to the existence in the chromosomes of determiners or genes. These have never been observed, nor is their nature known, but the evidence, derived both from a microscopic study of germ cells and from breeding results, indicates strongly that the genes are arranged in a row in each chromosome, and furthermore that the two members of a chromosome pair contain genes for corresponding contrasted pairs of characters, and that the genes are arranged in the same order in the two chromosomes.

It is also reasonably certain that during the maturation of the egg and sperm, while the two chromosomes of a pair are lying side by side in the synaptic union, there is interchange of parts between them, so that when they again separate in the maturation divisions a new combination of genes has been effected. When the chromosomes from two parents mingle in the fertilized egg, still other combinations of genes are produced. Thus maturation makes possible the production of different kinds of eggs and sperms by one individual whereas fertilization brings about the mingling of characteristics from two different parental lines.

Of interest in this connection are very extensive breeding experiments upon the small fruit fly, Drosophila, in which over 400 hereditary characters have been studied. These characters are linked together into four definite groups, corresponding to the four pairs of chromosomes found in the cells of the species. Furthermore, one of these groups, the sex-linked group, may be definitely assigned to a certain pair of chromosomes, the XY pair, and another small group probably belongs to a small, round pair.

Moreover, by determining the different percentages of inheritance

In either case two kinds of sperms would be produced. It is now becoming more generally agreed that both X and Y chromosomes are present, as expressed in the figures of Painter reproduced in Figs. 8

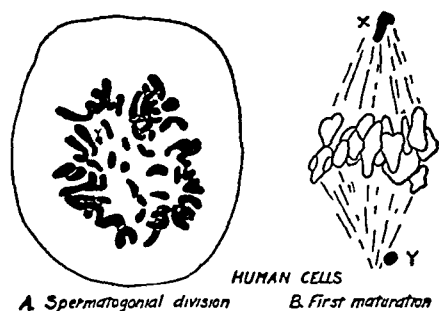


FIG. 8. Maturation of the human sperm. A, dividing spermatogonium showing 48 chromosomes. One of these is the small Y chromosome. The X cannot with certainty be recognized. B, first maturation division, showing the X and Y chromosomes already at opposite poles of the cell while the autosomes are still in the equatorial plate in the form of tetrads. (Redrawn from Painter, in *Jour. Exp. Zool.*, Vol. 37.)

and 9. The chromosomes of the human female have not been studied nor has human fertilization been observed, but in all probability the female number of chromosomes is forty-eight, including forty-six autosomes and two X chromosomes. The evidence seems complete enough that we may safely express the human condition by substituting for the autosomes of the opossum the larger human number of forty-six for the somatic cells and twenty-three for the sperms and mature eggs.

The chromosomes observed in human spermatogenesis serve well to show that chromosomes differ in size and shape and that they occur in pairs. Figure 9 shows the chromosomes from the equatorial plate in the spermatogonial mitosis which is shown in Fig.

8A, as they would appear if arranged in pairs in a row. Not all the pairs can be matched with certainty, but many of them can.

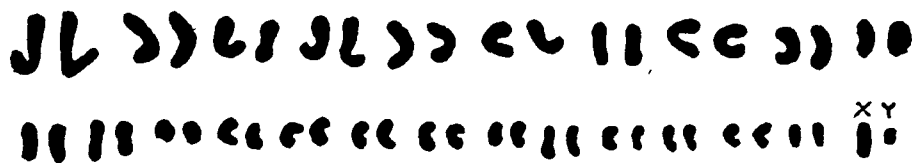


FIG 9. Human chromosomes. The 48 chromosomes shown in Fig 8A are drawn as they would appear when arranged in pairs of similar size and shape. (Redrawn from Painter, in *Jour. Exp. Zool.*, Vol. 37.)

C. THE IMPORTANCE OF MATURATION AND FERTILIZATION

In the foregoing account of maturation and fertilization, we have a striking example of the elaborate care with which small details of animal structure have been worked out. The behavior of the chromosomes at this time is, moreover, of the utmost importance because, as

previously indicated, the chromosomes seem to be the bearers of hereditary characteristics. Available evidence indicates that very probably they are responsible for the transmission from generation to generation of not only the stable characteristics which are common to all members of the species, but also the variability of structure and function which produces family traits and individual peculiarities. The successful accomplishment of the complex events of embryonic development in all probability depends upon the existence of a proper chromosome structure in the fertilized egg. The entire architecture of the adult body is accordingly, largely at least, predetermined by the composition of the chromosomes in the egg and sperm.

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Moreover, by determining the different percentages of inheritance

linkage between characteristics within each of the four groups, it has been computed in what order and at what relative intervals the genes are arranged along the chromosomes.

The significance of the preceding paragraphs can be fully appreciated only by persons familiar with the details of Mendelian inheritance, but the above statement will serve to convey to all readers some conception of the importance assigned to the chromosomes by students of heredity and development.

D. THE TWO RESULTS OF FERTILIZATION

1. Biparental Inheritance. In fertilization, as already seen, there is a union of two cells, egg and sperm, each with its reduced number of chromosomes. Fertilization thus restores the original number and the paired condition of the chromosomes. The importance of the union lies in the fact that by it the offspring inherits characters from both parental lines.

2. Stimulation to Development. By stimulating the egg to mitosis, fertilization also initiates the process of development. The eggs of some few animals, for example, the drone-producing eggs of the honey bee, develop without fertilization. This is known as **parthenogenetic development**. Many other eggs which do not ordinarily develop without fertilization can be induced to do so by chemical or mechanical means. For example, the eggs of many kinds of marine animals may be stimulated to the early stages of development by the addition of various substances to the water in which they lie. Frogs have been raised through the stage of metamorphosis from eggs stimulated by the prick of a needle.

These experiments in **artificial parthenogenesis** show clearly that the two phases of fertilization are independent phenomena — that the sperm produces two results upon the egg, one of which may be produced by other means. Thus young animals with only one parent may be produced, though no such have been carried to sexual maturity.

E. THE UNKNOWN CAUSE OF DEVELOPMENT

Although, as pointed out above, the chromosomes in all probability determine the course of development, the real *cause* of development is yet unknown. We do not know, after all, why an egg develops at all, nor why it develops along a definite line into an adult of the parental species. We merely say that it does so because it was produced by an animal of that species rather than by some other — that is, a human egg develops into a human being because it was produced

by a human being—a statement which really does not tell the reason at all

Yet the remarkable fact remains that within the small compass of the fertilized human egg, about 0.14 mm in diameter, there reside the possibilities of development into a complete human being, one having not only the peculiarities of the parental race, but also many inherited family traits of body and intellect. Though we know definitely that the sperm carries these characters from the father and the egg carries them from the mother, and there is good evidence that in the egg and sperm the chromosomes are responsible, it is not known by what chemical or physical peculiarities of the genes the development of the child is directed along predetermined lines. The nature of the genes is unknown, the riddle of development is still unanswered.

CHAPTER III

OVULATION, MENSTRUATION, AND PREGNANCY

It is necessary at this point to describe certain phenomena which, though not a part of embryonic development, are so intimately associated with it that the student of embryology must be informed about them, namely, those processes in the ovary and uterus without which reproduction and development could not take place.

A. OVULATION AND THE OVARIAN CYCLE

Ovulation, the discharge of the ovum from the ovary, should not be confused with oögenesis or maturation of the ovum, which has been described in Chapter II. Ovulation takes place in women during the years of sexual maturity at intervals of about twenty-eight days, though the interval is subject to variation in length. Ovulation may be looked upon as the climax of a regularly recurring cycle of events in the ovary, events which need be only briefly recounted here, because it is assumed that the reader is familiar with the details as described in textbooks on histology.

The ovarian cycle includes two main parts or phases: (1) The **follicular phase** includes the time when ova and follicles are growing rapidly. It occupies about the first half of the cycle and terminates with ovulation. (2) The **lutein phase**, beginning immediately after ovulation, is characterized by the development of the corpus luteum and ends with its degeneration. The termination of this phase is not sharply delimited from the beginning of the next follicular phase (Fig. 32, p. 52).

During each ovarian cycle several primary follicles undergo varying degrees of growth, but usually only one of them progresses to maturity and ovulation. The others undergo degeneration (atresia) at various stages of their growth. Growth and degeneration of ova and follicles begin before birth and are especially active during the early years of life but continue to the menopause. It is said that a primary follicle requires about ten to twelve days to develop to maturity. The primary ova are formed from the germinal epithelium covering the ovary. Many writers have believed that all the ova a woman is to have during her entire life are present in the cortex of the ovary at birth,

but a growing body of evidence indicates that even during the years of sexual maturity there are periodic migrations of cells from the germinal epithelium which give rise to new ova and follicle cells

After ovulation the ovum soon enters the fimbriated ostium of the Fallopian tube and thence goes to the uterus. Its fate there depends upon whether fertilization has taken place

In the formation of the corpus luteum the cells of the stratum granulosum of the ruptured follicle play the primary part. These cells enlarge rapidly and become filled with droplets of a yellow, fatty substance, lutein. The growth of these cells soon obliterates the follicular cavity with its coagulated hemorrhagic contents and before long produces a good-sized mass, the corpus luteum. At the same time the connective tissue cells of the surrounding theca folliculi also enlarge and assume an epithelioid form, resembling somewhat the lutein cells derived from the granulosa cells. They are known as theca lutein cells. In degenerating (atretic) follicles the theca cells undergo a similar development, forming masses of cells called corpora lutea atretica, but the granulosa cells of atretic follicles degenerate without forming lutein cells.

In the absence of pregnancy the corpus luteum reaches its greatest development about twelve days after ovulation, then rather quickly degenerates. In pregnancy it becomes a mass which may grow as large as 3 cm. in diameter and attains its maximum size at the fifth or sixth month. In either event the corpus luteum in due time degenerates, leaving in its place a mass of white fibrous tissue, the corpus albicans.

B MENSTRUATION AND THE UTERINE CYCLE

The uterus, like the ovary, is subject to important cyclic changes, affecting conspicuously the endometrium. The external manifestation of these changes is menstruation, the discharge of blood from the uterus at average intervals of about twenty-eight days, though the time is subject, even in healthy women, to considerable variation. Menstruation begins in young women at the time of puberty (age eleven to sixteen years) and continues until the menopause (age forty-five to fifty years). The first day of each menstrual flow is used as a point in time from which other events in the female sexual cycle are dated (Fig. 32, p. 52).

The complete menstrual cycle includes the following three phases:
(1) The menstrual phase of three to five days' duration is marked by hemorrhage and destruction of endometrial tissues. During this phase the endometrium decreases in thickness from as much as 5 mm. to

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The ovarian cycle includes two main parts or phases: (1) The **follicular phase** includes the time when ova and follicles are growing rapidly. It occupies about the first half of the cycle and terminates with ovulation. (2) The **lutein phase**, beginning immediately after ovulation, is characterized by the development of the corpus luteum and ends with its degeneration. The termination of this phase is not sharply delimited from the beginning of the next follicular phase (Fig. 32, p. 52).

During each ovarian cycle several primary follicles undergo varying degrees of growth, but usually only one of them progresses to maturity and ovulation. The others undergo degeneration (*atresia*) at various stages of their growth. Growth and degeneration of ova and follicles begin before birth and are especially active during the early years of life but continue to the menopause. It is said that a primary follicle requires about ten to twelve days to develop to maturity. The primary ova are formed from the germinal epithelium covering the ovary. Many writers have believed that all the ova a woman is to have during her entire life are present in the cortex of the ovary at birth,

animals, supplemented by observations upon women, it has become evident that the cyclic changes in the uterus are brought about by two hormones secreted by the ovary. (1) The cells of the growing ovarian follicles secrete the ovarian follicular hormone known as estrogen, as well as by several other names. Estrogen has the function of producing and maintaining the female secondary sexual characteristics and of causing normal development of the uterus and vagina. It also stimulates the denuded endometrium at the close of menstruation to undergo the regenerative process, which, we have already seen, is completed by the time of ovulation. The cells of the corpus luteum also continue to secrete estrogen for a time. (2) The specific function of the corpus luteum is the secretion of a second female sex hormone, which is known as progesterone and also called by several other names. Progesterone causes the regenerated endometrium to develop into the premenstrual or pregravid endometrium. If pregnancy does not occur, by the time the premenstrual endometrium has become well developed the corpus luteum begins to degenerate and its secretion to diminish. The withdrawal of the secretion of the corpus luteum allows the premenstrual endometrium to break down and menstruation to begin. About this time, however, another group of growing follicles begins the secretion of estrogen, which induces the regenerative process. Thus the cycle begins anew.

It is now known also that the ovary is in turn stimulated by two hormones secreted by the anterior lobe of the pituitary gland. (1) A follicle-stimulating hormone causes the growth of ovarian follicles and thus indirectly brings about the secretion of estrogen. (2) A luteinizing hormone causes the rupture of the ripe follicle (ovulation) and the development of the follicle cells into the corpus luteum. It is thus indirectly responsible for the secretion of progesterone. The cyclic nature of the ovarian response seems to be due to an interaction between pituitary and ovarian hormones. A further indication of the importance of the pituitary body in the reproductive process is the fact that removal of the anterior lobe is followed by atrophy of all reproductive organs in both sexes.

It is of interest that menstruation frequently occurs in rhesus monkeys without the occurrence of the ovulation which would normally precede it in the cycle. This phenomenon is also known to occur in women, but its frequency is not known. In such anovulatory cycles menstruation takes place from an endometrium of the interval type, produced under the influence of follicles none of which reach maturity. The premenstrual phase is not produced, inasmuch as no corpus luteum develops.

1 mm. or less. (2) The regenerative phase occupies seven to ten days and terminates about the middle of the menstrual cycle. During this phase the denuded endometrium becomes restored to normal structure, with glands for the most part straight and uniform in diameter. Mitoses are abundant. The endometrium attains a thickness of 2 to 3 mm. (3) The premenstrual or pregravid phase includes the latter half of the cycle (about fourteen days). During this phase the endometrium thickens to as much as 5 mm., the glands become tortuous and locally dilated, many of the blood vessels become much enlarged, and the stroma becomes edematous. The development of this phase prepares the endometrium for a possible pregnancy. The transition from the regenerative to the premenstrual phase is gradual and is often called the interval or mid-cycle.

Menstruation does not commonly occur during pregnancy; in fact its absence is one of the points used in the diagnosis of the condition and in computing the probable date of its termination. Neither does it occur for a few months following parturition, though the length of this time is variable.

It should be noted here that the epithelium of the vagina also undergoes cyclic changes during the menstrual cycle, though they are not at all comparable to those of the endometrium.

C. THE RELATIONS BETWEEN OVULATION AND MENSTRUATION

The time relation between ovulation and menstruation has, during recent years, been the subject of much careful investigation by many workers using various species of primates in diversified experimental procedures. Of great importance have been studies upon the rhesus monkey (*Macacus rhesus*), which have given highly dependable information, because the female sexual cycle of this monkey is so similar to the human cycle.

It has now been established beyond reasonable doubt that ovulation in women occurs most frequently about the middle of the menstrual cycle (thirteenth or fourteenth day), in the interval between the regenerative and premenstrual phases. This being the case, the follicular phase of the ovarian cycle corresponds to the combined menstrual and regenerative phases of the uterus, and the lutein phase of the ovary to the premenstrual phase of the uterus. That this relation is not a mere coincidence becomes apparent when we consider the means by which this coordination is now known to be brought about (Fig. 32, p. 52).

From a great amount of experimental work upon many species

implantation. It is present in the urine of pregnant women and is used as the basis of the Ascheim-Zondek and Friedman tests for pregnancy. It is in part a duplication of the anterior pituitary secretion, but the relations are so involved and so imperfectly known that very little should be said here. Nor is the exact importance of the corpus luteum of pregnancy fully understood.

An investigation of these matters is difficult because each species has its own peculiar reactions, and the results of experimental work on other species cannot always be directly applied to women, though such results do give indispensable clues.

The reader should not lose sight of yet other phases of the extensive series of coordinated reactions on the part of a pregnant woman, reactions necessary for the well-being of the infant both before its birth and during the few months immediately thereafter.

Among these changes are (1) growth of the uterus to contain the growing ovum, (2) a development of its muscular coats sufficient for the work of delivery, (3) increase of its blood supply for its own needs and those of the fetus, (4) development of the decidual membranes, (5) changes in the cervix and the vaginal canal which permit birth of the infant, (6) histological development of the mammary glands during pregnancy, (7) the beginning of lactation after delivery, (8) general and far-reaching physiological changes, (9) delivery, and finally (10) return to the structure and cyclic sexual function of the non-pregnant condition.

It is now generally recognized that the period of heat, or estrus, in animals which do not menstruate, such as dogs, cows, and rats, does not correspond to menstruation in women and female primates, but to the interval phase, the time when ovulation takes place. The slight bleeding in some species of animals at the time of heat does not correspond to the menstrual flow but to a slight intermenstrual uterine bleeding experienced by some women about the time of ovulation. In animals which do not menstruate, the hypertrophied endometrium undergoes regression without the hemorrhage of menstruation.

D. PREGNANCY

The two fundamentally important events of the ovarian and uterine cycles are the production of ova and the preparation of the uterine mucosa for the reception of the fertilized egg by the development of the premenstrual or pregravid condition. It is now rather generally agreed that, for pregnancy to occur, ovulation and coitus must occur about the same time, inasmuch as it has been shown that ova do not live more than a day or so after ovulation, nor do spermatozoa long retain their fertilizing power in the female genital tract. It is also reasonably certain that human ovulation is not brought about by coitus but occurs spontaneously at a fairly regular time, though the frequency and extent of departures from the usual time are not known.

Fertilization probably must take place within a day or less after ovulation. Development begins at once and continues during the passage of the ovum through the Fallopian tube and in the uterus, where it is at first nourished by the secretion of the endometrial glands. Implantation in the pregravid endometrium begins about the sixth day after ovulation (the twentieth day of the menstrual cycle) and is completed in about five days. Implantation is thus completed before the date of the expected menstruation (Fig. 32, p. 52).

When implantation takes place the expected breakdown of the pregravid endometrium does not occur, and the pregravid endometrium becomes the gravid endometrium from which the decidual membranes develop. Thus the usual cycles of endometrial changes are interrupted and are not resumed for some months after the termination of pregnancy. It must be remembered also that during this same time the cyclic changes in the ovary are suspended (Fig. 32, p. 52).

The modified behavior of the female sex organs during pregnancy is clearly due to a hormone produced by the chorion. This hormone may be demonstrated as early as the date when the expected menstruation fails to appear, that is, very soon after the completion of

are clearly seen in the embryo proper, but are less clearly defined in the human fetal membranes. The germ layers are the early tissues from which all adult structures are formed according to an orderly process, each germ layer giving rise to a definite set of tissues and organs.

2 The Embryonic Period This stage might be called the period of organ formation. In the closing days of the third week, the organs of the new individual begin to develop from the germ layers that were produced during the period of the ovum, and in approximately a week the body takes form. At first, it bears no resemblance to an adult human being, yet it has a definite, characteristic form. It is known as an embryo (Fig 22, p 45). During the embryonic period all the organs of the body originate, and by its close they are well established. The greater part of the matter presented in textbooks of human embryology deals with the events of this period, which, according to the chronology in general acceptance, lasts about five weeks. More recent, careful work, however, assigns only about three weeks to it (Table 1, p 54).

3 The Fetal Period During the eighth week, the developing individual assumes a form that is easily recognized as human, and henceforth until birth is properly designated as a fetus (Fig 26, p 47). During the fetal period the individual grows greatly and undergoes continued histological and anatomical development by which all parts of the body become more and more like those of the adult.

B SOURCES OF INFORMATION ABOUT EARLY HUMAN DEVELOPMENT

The beginning of sound knowledge of early human development does not date back many decades. Embryos for study of early human development have come mostly from autopsies and operations. Some of the specimens so secured were abnormal, some were poorly preserved, and others were inadequately described. Some of them, however, were excellent in every respect and were clearly described. These have served as a solid basis for growing knowledge of early human development. In the search for younger and younger human embryos a few outstanding examples, each of which has for some years enjoyed the distinction of being the youngest, have come to light.

Conspicuous among these "youngest" embryos are Spee's embryo Gle in 1889 (nineteen days) (Fig 15F), Peters' embryo in 1899 (fourteen days) (Figs 14 and 15E), the Bryce-Teacher embryo in 1908 (thirteen days), and Miller's embryo in 1913 (eleven days).

CHAPTER IV

EARLY STAGES OF HUMAN DEVELOPMENT

The embryonic development of vertebrates follows a general plan which is fundamentally similar in all groups. Each group, however, be it a species or one of the broader divisions, has also its own special developmental peculiarities. Although much can be learned about human development by study of other species, some points can be learned only from human embryos. This is especially true in the early stages of human development, and it is only very recently that persistent studies have accumulated sufficient information so that a direct account of early human development may be written. The treatment in this chapter is, so far as possible, such a direct account, with only a minimum of reference to other species.

A. THE THREE STAGES OF HUMAN PRENATAL DEVELOPMENT

Prenatal life may be conveniently divided into the following three periods: (1) the period of the ovum, (2) the embryonic period, and (3) the fetal period (Fig. 32, p. 52).

1. **The Period of the Ovum.** The period of the ovum includes approximately the first three weeks. The body of the new individual does not begin to form during this period, the time being occupied in the production of primitive, embryonic tissues, notably the three germ layers from which the embryo is to develop. The developing ovum also establishes adequate nutritive relations with the uterine mucosa. The period of the ovum may be subdivided into two parts.

a. Cleavage. During the earlier part of development the most conspicuous activity is cleavage, or cell division, by which numerous cells are produced from the single fertilized ovum (Fig. 10). Of course, cell division continues actively as long as the individual is growing and even, to a lesser extent, in adult life. But in these later stages it is less evident than during early development.

b. *The Formation of the Germ Layers.* As the cells multiply they begin to specialize, some earlier than others, and to arrange themselves according to a definite structural plan. By this plan the cells form the three germ layers, ectoderm, entoderm, and mesoderm, which

are clearly seen in the embryo proper, but are less clearly defined in the human fetal membranes. The germ layers are the early tissues from which all adult structures are formed according to an orderly process, each germ layer giving rise to a definite set of tissues and organs.

2 The Embryonic Period This stage might be called the period of organ formation. In the closing days of the third week, the organs of the new individual begin to develop from the germ layers that were produced during the period of the ovum, and in approximately a week the body takes form. At first, it bears no resemblance to an adult human being, yet it has a definite, characteristic form. It is known as an embryo (Fig 22, p 45). During the embryonic period all the organs of the body originate, and by its close they are well established. The greater part of the matter presented in textbooks of human embryology deals with the events of this period, which, according to the chronology in general acceptance, lasts about five weeks. More recent, careful work, however, assigns only about three weeks to it (Table 1, p 54).

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(like Figs. 13 and 15D). Descriptions and illustrations of these four embryos have been widely used in textbooks of human embryology.

The determination of the ages of early embryos has not been easy, and some of the earlier specimens, when first described, were thought to be much younger than they are now known to be. During recent years more accurate estimation of ages has been made possible by better knowledge of the female reproductive cycle, by an increasing number of human embryos for comparison, and by careful study of young embryos of monkeys.

In the past two decades knowledge of the human embryo has grown rapidly because of improved technics and cooperative facilities. Many excellent young human embryos have been described, thus making the sequence more complete by narrowing the gaps in the series. Among these recent embryos are at least four that are younger than any previously described. All are less than eleven days, the youngest being estimated at seven and one-half days (Fig. 12). Though studies of recent years have removed many uncertainties, unanswered questions still remain. Fortunately the remaining gaps may be bridged with considerable certainty by recent careful observations on the embryos of other mammals, notably the rhesus monkey (*Macacus rhesus*), whose early development in most respects closely parallels that of the human being. The main portion of the following account is based upon human embryos but is supplemented and interpreted where necessary with information derived from other species.

C. THE FREE OVUM IN THE FALLOPIAN TUBE AND UTERUS

The human ovum is normally fertilized in the Fallopian tube, which it enters shortly after its discharge from the ovary. If it is not fertilized within a few hours, it begins to degenerate. If it is fertilized, development begins at once and continues during the journey of about three days through the Fallopian tube and during the few days while the ovum is free in the lumen of the uterus. It is during this early, free period that human development has not been observed, and this gap must be filled with information from other species, inasmuch as the youngest human embryo known is already partly imbedded.

It will be remembered that the ovum, when discharged from the ovary, is surrounded by the zona pellucida, a non-living, homogeneous membrane which is not part of the ovum. Early stages of development are passed within this envelope (Figs. 10 and 11). The membrane doubtless serves to protect the ovum and to hold the early cells together. It also prevents the ovum from making premature contact with the mucosa of the tubes and uterus.

The first division of the fertilized ovum, as seen in the living ova of the rhesus monkey studied microscopically in a culture medium, takes place about twenty-four hours after ovulation, and the next few divisions follow each other at intervals of about twenty-four hours, so that at ninety-six hours (four days) four divisions have been completed, making sixteen cells of about equal size, arranged as a solid ball known as a morula (Fig 10) Human cleavage is doubtless comparable

As cell multiplication continues beyond the sixteen-cell stage, it is not long until the outermost cells begin to flatten against the inner surface of the zona pellucida to form a rather definite layer, the trophoderm. The interior cells, not in contact with the zona, form the so-called inner cell mass (Fig 11A) The next obvious change is a separation between the inner cell mass and the trophoderm, begin-



FIG 10 Early cleavage of the ovum of the monkey, *Macacus rhesus* Enlarged photographs from motion picture film of living ova show 2-, 4-, 8-, and 16-cell stages All were still surrounded by zona pellucida, shown only in 2-cell stage Unsuccessful spermatozoa and polar bodies shown in 2-cell stage (After Lewis and Hartman, in *Cont to Emb*, Carnegie Inst)

ning at one side and producing a crescent-shaped cavity filled with fluid (Fig 11B) As the fluid increases in amount, the trophoderm grows, and the cavity becomes deeper and expands laterally, leaving the inner cell mass attached to the trophoderm at one side only During the expansion of the trophoderm its cells become flattened, and the surrounding zona pellucida stretches and becomes thinner The ovum at this stage is called a blastocyst or blastodermic vesicle (Fig 11C)

During the development of the blastocyst, the cell divisions become less uniformly timed than during the early cleavage stages, with the result that the cells become conspicuously different in size as well as in shape Cell differentiation is already under way

This early cell differentiation is shown clearly in a monkey ovum which is not yet attached to the wall of the uterus (Fig. 11C). In this ovum there are 140 cells. In the wall there are fifty-eight very thin trophoderm cells which form a delicate membrane enclosing the blastocyst cavity. There are also fifty-six other trophoderm cells c

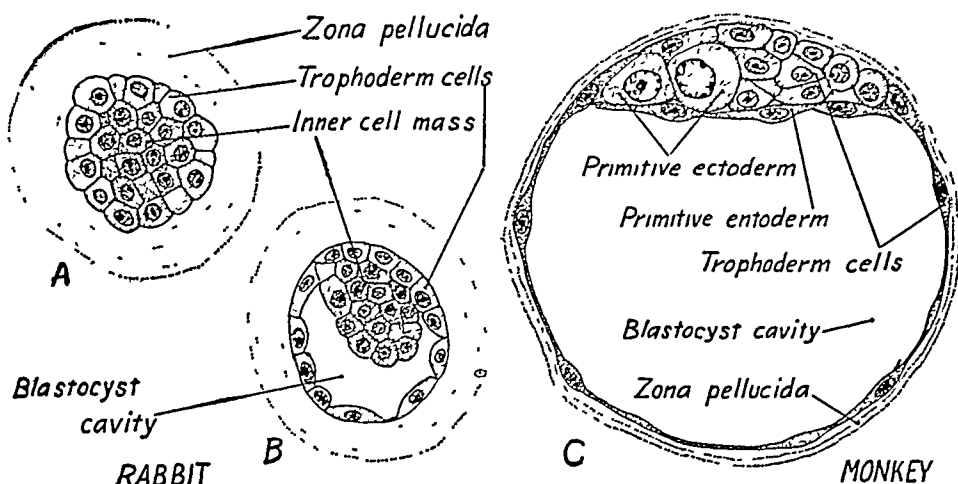


FIG. 11. The development of the blastocyst: A and B, rabbit ova. (Gregor in *Cont. to Emb.*, Carnegie Inst., Washington.) C, the free blastocyst of the monkey, *Macacus rhesus*, about a day before implantation. (Heuser and Streeter in *Cont. to Emb.*, Carnegie Inst., Washington.)

irregular shapes, grouped in the region of the inner cell mass. These 114 trophoderm cells are destined to form, not part of the embryo proper, but rather the extra-embryonic membranes which are cast off at birth.

In the inner cell mass there are fourteen cells much larger than any of the others. They have not divided as often as have the smaller cells and are still in a more primitive state. They may be called primitive ectoderm cells, though the name is not completely accurate. On the lower surface of the inner cell mass, bordering the blastocyst cavity, there are twelve rather flattened cells, the primitive entoderm. It is from these two groups of twenty-six cells that the embryo proper will develop, though possibly part of the extra-embryonic membranes may also come from them. It is interesting to note that even at this early stage of development there has been a differentiation between embryonic and extra-embryonic structures. Though the free human blastocyst has not been observed, it is doubtless very similar to that of the monkey just described. It is at a stage about like this one that implantation begins.

J THE EMBRYONIC DISC OR SHIELD

The Primitive Streak and the Embryonic Mesoderm Mesoderm in the embryonic area forms entirely independently of the early extra-embryonic mesoderm. The first mesoderm cells in the embryonic area appear about the fifteenth day. They are produced by division of cells of the germ disc, which then migrate downward into the space between ectoderm and entoderm. Soon the migration of mesodermal cells becomes sharply localized in a narrow longitudinal band in the posterior end of the germ disc. This is the primitive streak (Figs 15, 16, and 18). The mesoderm from the primitive streak forms two sheets which spread out laterally between ectoderm and entoderm, thus forming the third of the germ layers, which is more fully described in Chapter VII.

The Embryonic Disc The three-layered wall between the amniotic cavity and the yolk sac is the embryonic shield or disc. From it the embryo develops. During the closing days of the third week, several important structures foreshadowing the formation of the embryo have their beginning here. The general process of embryo formation is described in Chapter V.

K EARLY VASCULAR PRIMORDIA

A highly significant item of development during the third week is the beginning of the blood vascular system. Though actual circulation of blood does not begin until about the middle of the fourth week, the preliminary development of blood has its start at the beginning of the third week. The cell groups that will develop into blood vessels are distinguishable first in the mesoderm of the chorion and its villi, and a little later in the body stalk and in the mesodermal layer of the yolk sac (Fig 15F). These primordia, all extra-embryonic in position, are slowly developing even before the embryonic disc is formed, and as development of the disc progresses, vascular primordia come to be included in it. Fuller details are given in Chapter XIV.

L SUMMARY

It may be seen from the foregoing account that, during the period of the ovum, the greater part of the growth is in the extra-embryonic structures which do not enter into the formation of the embryo proper. It is also evident, however, that preparation is made for the future development of the embryo, the embryonic disc is formed, with its three germ layers, those simple tissues which later serve as materials for the elaboration of the more complicated organs of the

embryo. In human development the three germ layers are involved also in the development of the extra-embryonic membranes, but it should be noted that the layers in the structures are derived, mainly at least, from the trophoderm, whereas those of the embryonic disc develop from the inner cell mass.

It should again be noted that not only does the developing ovum accomplish great structural differentiation during the period of the ovum, but a many-fold increase in the amount of actual living substance occurs, the increase being brought about through assimilation of necessary substances from the surrounding uterine tissues. The embryo not only develops; it lives and grows. At each stage of development it must be able to maintain necessary life activities in relation to its environment, just as must any adult organism. At all times during development, accordingly, two sets of structural features are to be recognized, the one related to the immediate needs of the embryo, such as the fetal membranes, the other to the developmental program. And, inasmuch as living and developing must be accomplished within the limits set by the framework of the inherited ancestral constitution of the ovum, there is introduced a third set of structural peculiarities, not obviously related to either of those needs, which can be explained only as relics of various ancestral characteristics and which may be observed in species lower in the evolutionary scale, for example, the embryonic pharynx and the plan of the embryonic circulation. Often the lines between the three cannot be drawn sharply, and the mechanics of development present many puzzling problems. Nevertheless it will be helpful to keep in mind the three kinds of structures while tracing development as presented in this book.

CHAPTER V

THE DEVELOPMENT OF THE EXTERNAL FORM

In Chapter IV the course of human development was traced through the period of the ovum up to the time when the embryonic disc is just beginning to develop into the embryo. It was seen that the embryonic disc is formed by about the middle of the third week as a flat

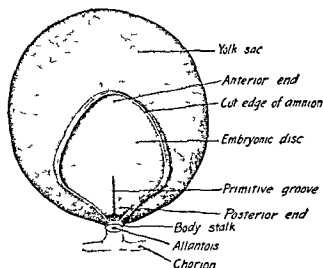


FIG 16 The Mateer embryo (about 17 days) as seen from above with the chorion and amnion removed (Redrawn from Streeter in *Cont to Emb*, Carnegie Inst, Washington)

structure composed of the three germ layers, ectoderm, mesoderm, and entoderm (Fig 15F). The embryonic disc has a somewhat elliptical outline, as seen in the Mateer ovum, (Fig 16). Anterior and posterior ends are recognizable in the embryonic disc, the posterior end being toward the body stalk.

A HOW THE EMBRYO ORIGINATES

Certain important features make their appearance very early in the embryonic disc. The primitive groove in the posterior region is the external manifestation of the primitive streak mentioned in Chapter IV (Figs 15 and 16). The neural groove is a broader longitudinal furrow extending forward from the anterior end of the

primitive groove. It forms the beginning of the nervous system and, after folding in, develops directly into the brain and spinal cord

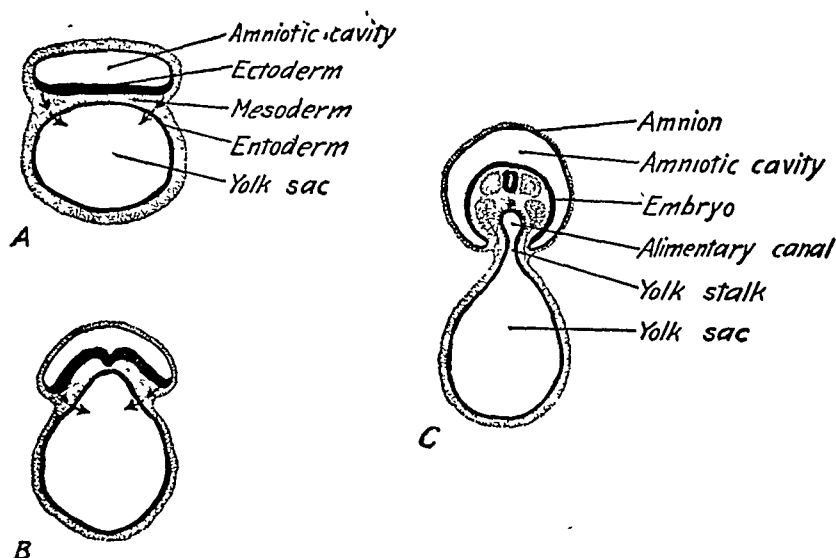


FIG. 17. Diagrammatic cross-sections to show the manner of formation of the human embryo. The chorion is omitted. *A*, the embryonic disc about as in the Peters ovum; the arrows show the direction of folding. *B*, the arching of the embryonic disc has begun. *C*, the body of the embryo has formed; the mode of formation of the amnion and yolk sac is also shown.

(Figs. 18, 19, and 20). The **neurenteric canal** is an opening at the anterior end of the primitive streak, which connects between the

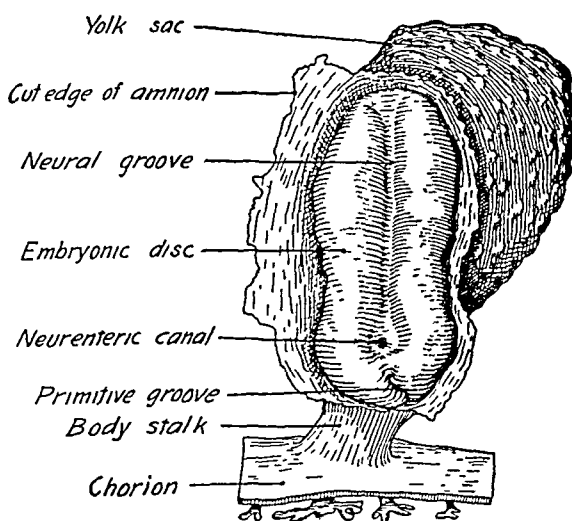


FIG. 18. Dorsal view of Spee's embryo *Gle*, 154 mm. long (19-20 days).

amniotic cavity and the yolk-sac cavity (Figs. 15*F* and 18). It lasts only a very short time and does not give rise to any adult structure.

The actual formation of the embryonic body from the embryonic disc is accomplished by more rapid growth of the disc along its longitudinal axis than at the margin. Thus, as it grows, it becomes thicker and at the same time is elevated along the mid line, forming an elongated arch (Fig 17A and B). The arching increases until the two sides come together at the bottom to form a hollow cylindrical structure covered with the ectoderm of the embryonic disc. Its interior cavity, the alimentary canal, is lined with the gut endoderm from the lower surface of the disc, and it communicates with the yolk sac by the narrower yolk stalk (Figs 15 and 17C). This process of

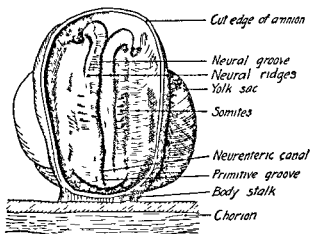


FIG 19 Dorsal view of Kromer's embryo K1b, length 1.8 mm (early part of fourth week) (From Keibel and Elze's *Normentafeln*)

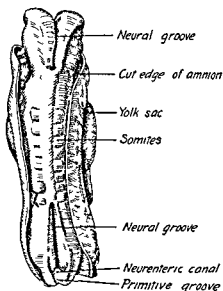


FIG 20 Dorsal view of Eternod's embryo, 21 mm long (nearly 4 weeks) (From Kollmann's *Hand atlas*)

growth and folding begins first at the anterior end, forming the head fold and the fore gut (pharynx) (Fig 15F). A little later, a similar folding begins at the posterior end. Thus the two ends of the embryo are early established (Figs 19 and 20). The folding process progresses from both ends toward the mid region, where the yolk stalk remains as a connection between the embryonic gut and the yolk sac (Figs 21 and 22). During the formation of the embryo as described, the amnion and the amniotic cavity become wrapped around the developing embryo, forming a fluid-filled, protective membrane (Figs 17C and 38, p 62).

The development of the external form of the embryo is clearly shown

in Figs 18 to 26, from which it is seen that, though the embryo is roughly cylindrical, it manifests some pronounced irregularities of

contour which give it a characteristic form. At first it has no resemblance to a human being and is called an **embryo**. At about the end of the eighth week it rather rapidly assumes human form and is henceforth, until birth, known as a **fetus** (Figs. 25 and 26).

B. VARIOUS EXTERNAL FEATURES

The Head. The head very early attains considerable size, inasmuch as the anterior end of the body develops more precociously than the posterior parts. During the embryonic weeks the brain dominates the shape of the head, inasmuch as it very early attains considerable size and is surrounded by only a thin layer of other tissues (Figs. 22 to 24).

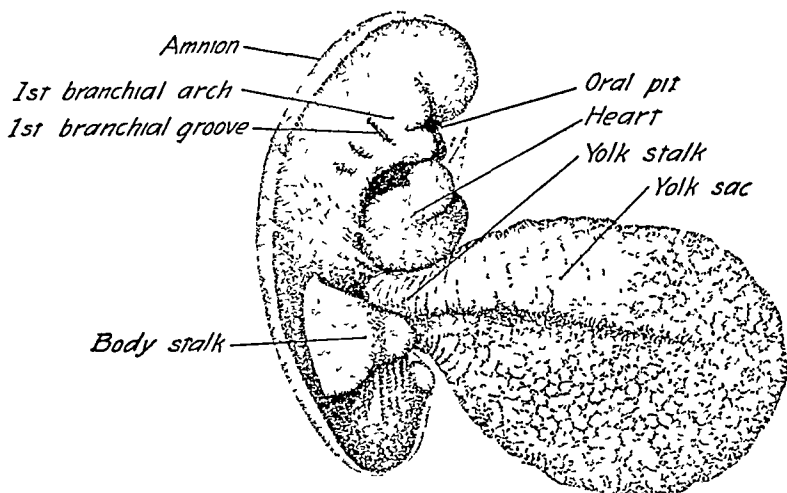


FIG. 21. Side view of embryo 2.6 mm. long (little more than 4 weeks), showing also amnion and yolk sac. (After His.)

The Somites. The embryos pictured in Figs. 19 to 24 show a row of elevations on each side of the neural groove and tube. These elevations are due to masses of mesoderm, the **somites**, underneath the ectoderm. From the somites there develop the vertebrae, the ribs, and the muscles of the trunk. The anterior somites are the first to form, and new ones are added posteriorly. The first somites form about the beginning of the fourth week. They increase in number with the age of the embryo, until the full number, forty-one, is reached. The anterior four somites are included in the head, from which it can be seen how large a part of the early embryo belongs to the head. The segmented axis of the embryo terminates posteriorly as a well-

developed tail, which in the adult is represented by the coccygeal vertebrae (Figs 23 and 24)

With the attainment of fetal form, the somites become indistinguishable on the exterior, having developed into muscular and bony structures which make no external, segmental prominences (Figs 25 and 26)

The Branchial Arches and Grooves A very conspicuous and characteristic feature of the embryo is a series of alternating ridges and furrows, the branchial arches and branchial grooves, on each ventro-

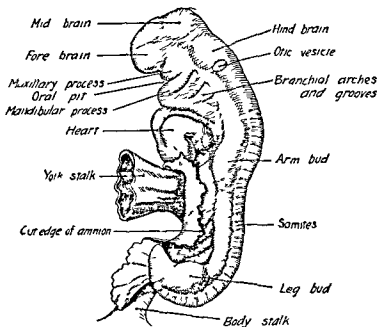


FIG 22 Human embryo 4.2 mm long (about 4½ weeks) (After His)

lateral side of the head (Figs 21 to 24), which first appear during the fourth week. They lie in the region of the **pharynx**, a portion of the embryo which gives rise to important structures belonging to several systems of organs. The branchial grooves correspond to the gill slits of fishes, through which the respiratory water current passes. In human development the grooves do not normally become perforated.

The first arch early develops two prominences, the **maxillary** and **mandibular** processes, which represent the upper and lower jaws. On the antero-ventral aspect of the embryonic head is the **oral pit**, a depression which is the precursor of the mouth (Figs 21 to 26). It is bounded partially by the maxillary and mandibular processes. The first branchial groove develops into the external auditory canal, and outgrowths of the first and second arches which border it become the

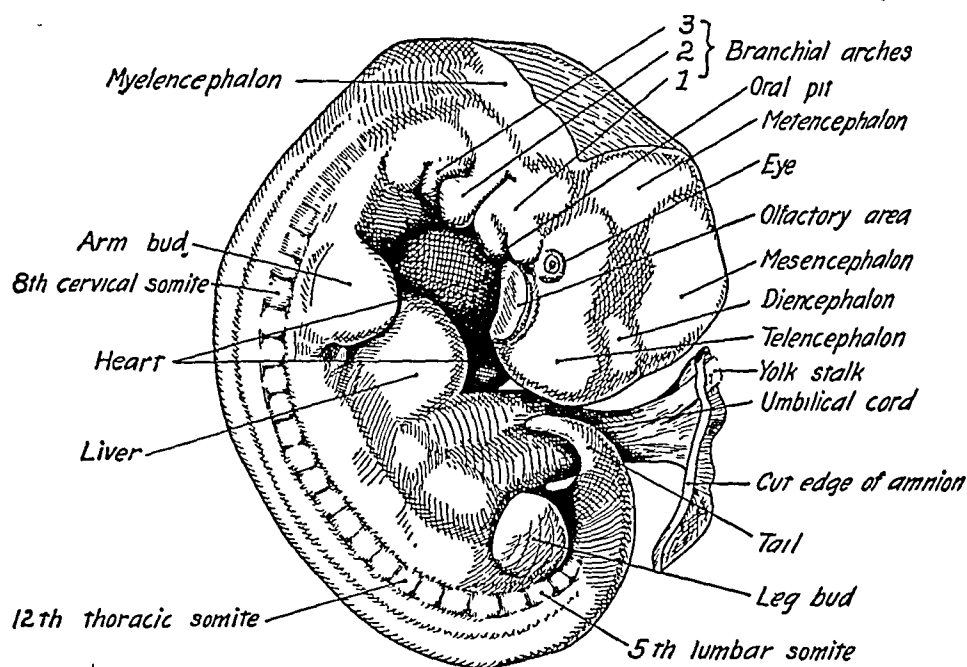


FIG. 23. Human embryo 7 mm. long (more than 5 weeks). (After Mall in *Jour. Morph.*)

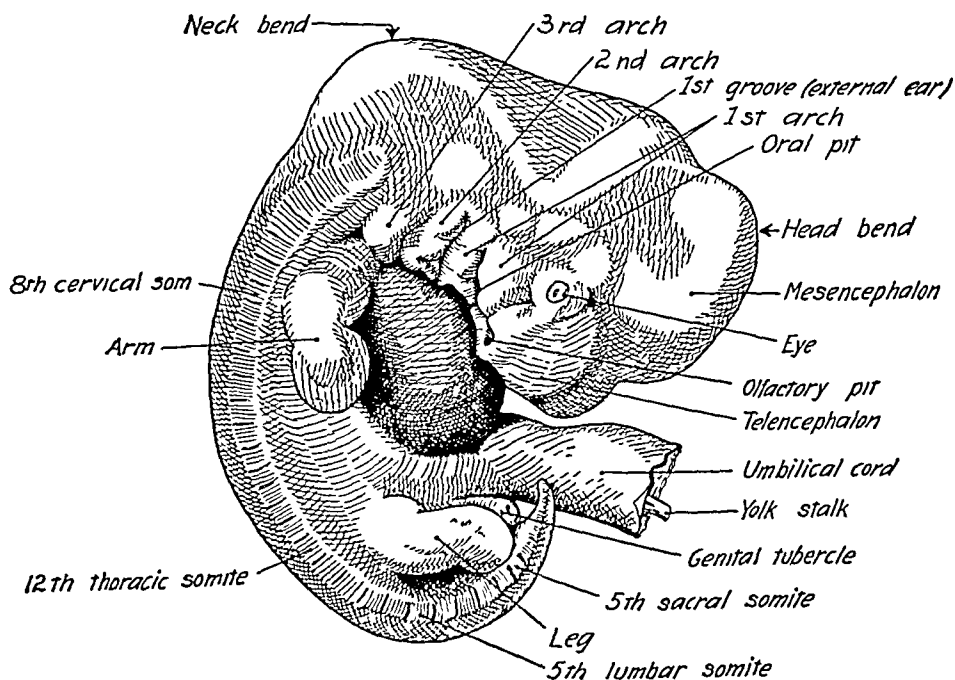


FIG. 24. Human embryo 105 mm. long (about 6 weeks). (From Kollmann's *Handatlas.*)

external ear (Figs 24 to 26 and 183, p 272) Early in the sixth week the fourth and fifth arches begin to sink below the surface, forming a pit, the cervical sinus, which soon becomes enclosed by overgrowth from adjacent areas. Normally the sinus promptly disappears, and all external evidence of the arches and grooves is lost (Figs 24 and 25)

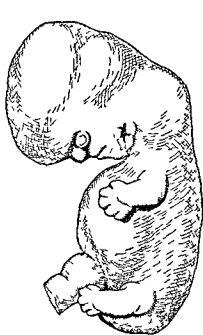


FIG 25 Human embryo 15.5 mm long (nearly 7 weeks) In transition from embryonic to fetal form. (After His)



FIG 26 Human fetus 23.5 mm long (about 8 weeks) Shows definitely the human form and marks the beginning of the fetal period (After His)

The Limb Buds The primordia of the arms and legs appear during the fourth week as two pairs of low elevations, the limb buds, which gradually elongate to form the cylindrical arms and legs. In a few days they develop paddle-shaped expansions at their free ends, in which the digits appear during the eighth week (Figs 22 to 26)

The Heart The embryonic heart, though not an external organ, develops by the fourth week into a large organ which makes a good-sized prominence on the ventral side of the embryo in the region of the head and neck (Figs 21 and 24). It remains one of the conspicuous features affecting external contour until the attainment of fetal form, at which time it recedes caudally into the thorax.

The Neck With the recession of the heart into the thorax, the constriction known as the neck appears. Its appearance is one of the conspicuous features in the transformation from embryonic to fetal form (Figs 24 to 26)

The Eye. The development of the eye involves both external and internal changes. It is sufficient now to note its appearance as an external feature during late embryonic life (Figs. 23 to 26).

The Flexures of the Embryo. Although the embryo is at first nearly straight, it soon becomes curved, being concave toward the ventral side until, early in the fifth week, the two ends nearly or quite meet (Figs. 21 to 24). The curving is decidedly abrupt in two regions, cephalic and cervical (Fig. 24). The flexures largely disappear during the attainment of fetal form (Figs. 25 and 26).

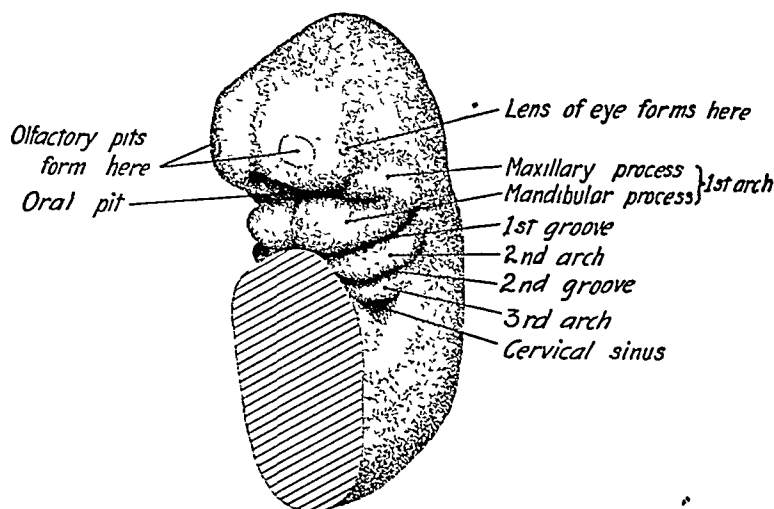


FIG 27. Head of human embryo 6 mm. long (about 5 weeks). The first of a series to show the development of the face. (Redrawn from Streeter in *Cont. to Emb.*, Carnegie Inst., Washington)

The Face. The development of the face, especially the mouth and nose, affords a striking example of the way in which structures of the embryonic period become transformed into those of the fetal and adult type. This change has already been observed in a general way (Figs. 24 to 26). Its details will be more fully understood by study of Figs. 27 to 31 in connection with the following descriptions.

The oral fossa or pit (properly called the *stomodeum*) is the first indication of the oral and nasal cavities. It is present in an embryo 2.6 mm. long (Fig. 21) and is well shown in one of 6 mm. (Fig. 27). It is bounded above by the fore brain region of the head, below by the mandibular process of the first arch, and laterally by the maxillary processes, which do not meet in the mid line (Fig. 27).

The mandibular processes unite in the mid line and so develop directly into the lower jaw. This development is readily understood by study of Figs. 27 to 30. The manner of formation of the upper jaw

and the nose is more complicated, involving the maxillary processes and the naso-frontal process. The naso-frontal process is a downward growth from the front of the head (Fig 28)

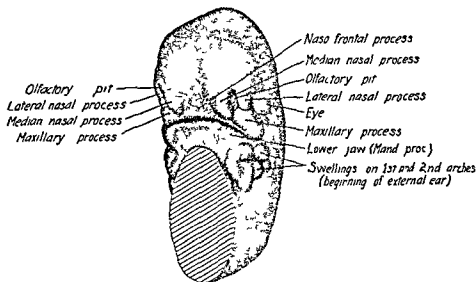


FIG 28 Head of human embryo 12 mm long (about 6 weeks) (Redrawn from Streeter)

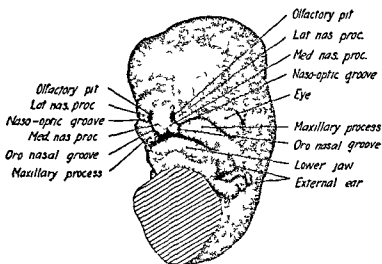


FIG 29 Head of human embryo 14 mm long (about 6½ weeks) (Redrawn from Streeter)

Early in the transformation of these structures, two thickened areas of ectoderm, the olfactory placodes, form on the sides of the naso-frontal process. Soon they become depressed to form the olfactory pits (Figs 27, 28, and 86, p 128). Each olfactory pit lies between two swellings of the naso-frontal process, the median and lateral nasal proc-

esses. The olfactory pits become circumscribed by the fusion of the ends of the median and lateral nasal processes with each other and are then known as the external nostrils (Figs. 29, 30, and 86, p. 128).

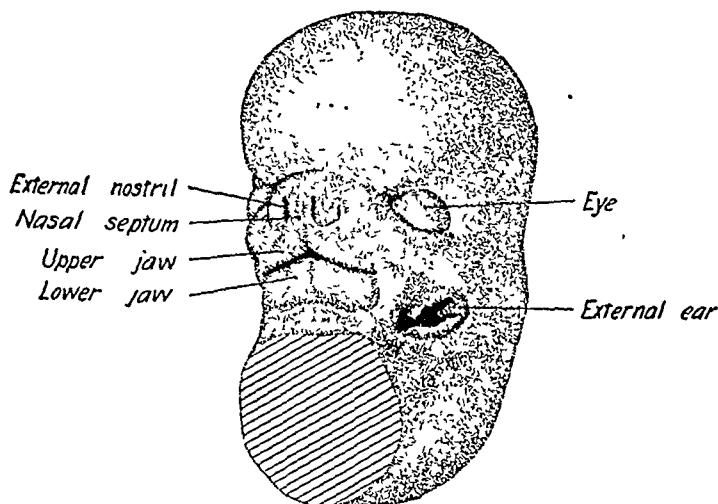


FIG. 30. Head of human embryo 18 mm. long (about 7 weeks). The parts of the adult face have formed but are not yet distinctly of the human form. (Redrawn from Streeter.)

At the same time the front margin of the upper jaw is completed by the fusion of the maxillary processes with the median nasal processes (Figs. 28 to 31). From the naso-frontal process develop the nasal septum, the philtrum of the upper lip, and the part of the jaw

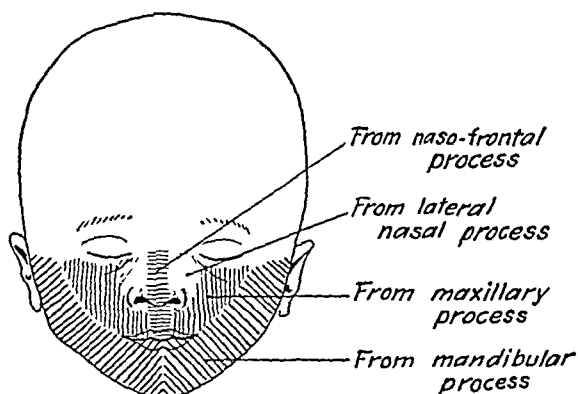


FIG. 31. Outline drawing of front view of face of fetus, shaded to show origins of certain parts of face.

bearing the incisor teeth (the premaxilla of some mammals). From the maxillary processes come the more lateral parts of the jaw and the lip.

The changes just described complete the formation of the face, as

seen in Fig 30, which shows all the adult features, though the face is not yet of distinctly human form. Certain changes in shape are now quickly accomplished, and by the early part of the seventh week the features are definitely human (Fig 26). Figure 31 shows the face of a fetus with differential shading to indicate the areas which develop from each of the embryonic structures described in the preceding paragraphs.

It will be observed that during the changes just described, the branchial arches, so pronounced in the embryo, disappear except as they are represented in the jaws and the external ear. Likewise the grooves are obliterated, except the part of the first which persists as the external auditory meatus (Figs 27 to 30).

C THE DURATION OF PREGNANCY

In the practice of obstetrics it is of great importance to be able to predict the date on which delivery may be expected. To do so one must know (1) the length of time required for the developmental process (the length of gestation) and (2) the date of its beginning.

Development begins with fertilization, but there is no way of knowing just when that event takes place. Moreover it is only in rare cases that the date of fruitful coitus is known. For this reason it is impossible to fix definitely the time when development begins, and a pregnant woman seldom suspects the existence of the condition until the expected menstruation fails to appear.

In obstetrical practice, therefore, pregnancy is assumed to begin on the first day of the last menstrual period. Experience has shown that delivery may be expected, on the average, ten lunar months (280 days) after that date, though it is well known that normal delivery may occur somewhat earlier or may be delayed beyond the expected time. There is at present a growing belief that the duration of pregnancy in reality includes the time of ten menstrual cycles and that it is longer in women with long cycles than in women with short ones. It is stated that during pregnancy the uterus undergoes mild muscular contractions at intervals corresponding to the time of menstruation. At such times premature births are most likely to occur, and at the tenth contraction period normal delivery is to be expected.

Though the beginning of the last menstrual flow furnishes a useful date for the obstetrician in computing the probable time of confinement, it does not give a measure of the actual age of the embryo, a matter of importance to the embryologist. As was pointed out in Chapter III, fertilization, in all probability, occurs within twenty-four hours after ovulation. Moreover, ovulation is now known to occur

most frequently about the middle of the menstrual cycle, that is, about two weeks after the beginning of a twenty-eight-day cycle. Wide departures from this average time are, however, known to occur, and added uncertainty is brought about by considerable variation in the length of the cycles. Embryologists, nevertheless, find it useful to express the ages of embryos as the *ovulation age*, which is about two weeks less than the *menstrual age* and is very close to the *actual developmental age* as measured from fertilization. The actual average duration of pregnancy is, accordingly, about thirty-eight weeks or nine and one-half lunar months (266 days). The age relations discussed in the foregoing paragraphs, together with other facts about the ovarian and menstrual cycles in relation to the events of pregnancy, are shown graphically in Fig. 32.

D. DETERMINATION OF THE AGE OF EMBRYOS

It is often highly desirable to know the age of an embryo or fetus which has been born prematurely or removed operatively. In determining the age of embryos it is necessary to consider (1) the duration of the pregnancy as indicated by skipped menses and (2) the size and degree of development of the embryo.

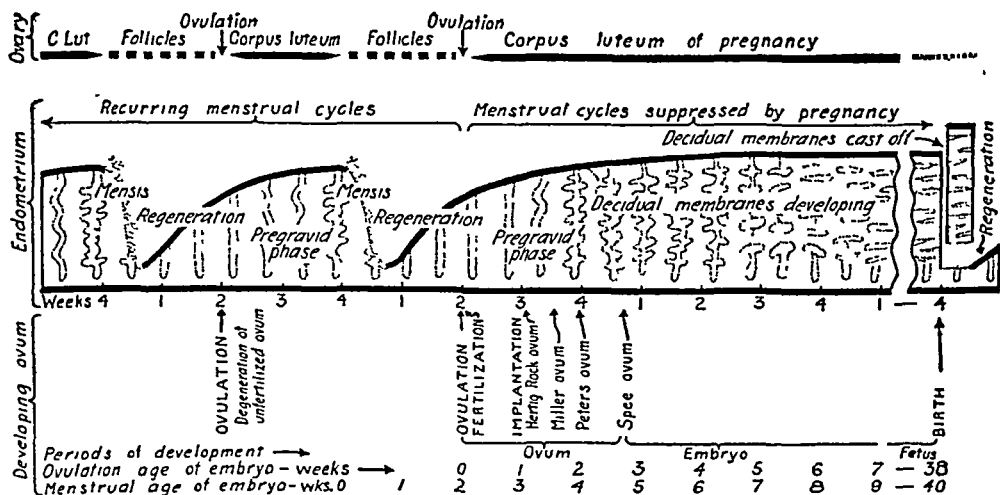


FIG. 32. Diagram showing the time relations between the ovarian cycle, the menstrual cycle, and the progress of pregnancy. The graph indicates the changing thickness of the endometrium and the varying form of the uterine glands. (Partly after Schroeder.)

In estimating the age of an embryo or the probable date of confinement it should be remembered that menstruation sometimes occurs one or more times after fertilization, causing an underestimation of the

age by one or more months. Moreover, premature infants are often dead in utero for some days before their birth, a condition which presents another source of uncertainty.

The age of an embryo may be judged fairly well by comparing its size with carefully prepared tables giving average sizes at frequent age intervals, such as Table 1. In using such tables it must be remembered that size is subject to variation before birth just as it is after birth. The degree of development is probably subject to less variation than is the size, certain features making their appearance at rather definite times, though development also is subject to variation. In Chapter XX is given a schedule of development which includes statements of the ages at which important structures appear. The best estimate of the age of a given embryo can be arrived at by considering together all the available evidence, including the history of the case, the size of the embryo, and its structure.

In measuring the lengths of embryos and fetuses, embryologists usually employ the **crown-rump length (CR)**. In embryos this is the distance in a straight line from the highest point of the mid brain to the lowest part of the sacral bend (Fig. 23). In fetuses, it is the sitting height. Obstetricians more commonly use the **crown-heel length (CH)**, which in fetuses is the standing height and is not applicable to embryos. In the pages of this book, lengths of embryos are given as crown-rump length.

The determination of the age of human embryos is a problem which has received much study by many capable men, but progress has been slow. Since 1910 the growth scale of Mall (Table 1) has been used extensively by American embryologists. A more recent scale, and no doubt more accurate, is that of Streeter. This scale is based upon very careful study of human embryos and is receiving added support by comparisons with accurately timed embryos of the rhesus monkey. As will be seen from Table 1, the newer scale differs from its predecessor in assigning earlier ages to the attainment of certain lengths and stages of development, especially during the embryonic period and the earlier fetal weeks. It allows only about three weeks, instead of the customary five, for the period of the embryo, the fetal form being attained about the close of the sixth week (ovulation age) instead of the eighth. Both scales are given in Table 1, but the age references throughout this book are the values of Mall, because they are the ones the student will most frequently meet in his general reading. Inasmuch as both the sizes and ages of embryos usually are given in the text, no confusion need result.

TABLE 1
THE GROWTH OF THE EMBRYO

Menstrual Age, weeks	Ovulation Age, weeks*	Crown-Rump Length, mm.		Weight, grams	Progress of Development
		Mall†	Streeter‡	Streeter	
1					
2					
3	1				Period of Ovum
4	2				
5	3				
6	4	2 5	6 5		Period of Embryo
7	5	5.5	12		
8	6	11	23	1.1	
9	7	17	31	2 7	Period of Fetus
10	8	25	40	4.6	
11	9	32	50	7.9	
12	10	43	61	14 2	
14	12	68	87	45	
18	16	121	142	198	
22	20	167	186	460	
26	24	210	228	823	
30	28	245	265	1323	
34	32	284	302	2074	
38	36	316	341	2914	
40	38	336	362	3405	

* In this table the ovulation ages are given as two weeks less than the menstrual ages, which is doubtless a close approximation of the true average difference.

† F. P. Mall, in *Human Embryology*, Keibel and Mall, 1910.

‡ G. L. Streeter, in *Cont. to Emb.*, Carnegie Inst., 1920, and an unpublished scale by the courtesy of Dr. Streeter.

E. TWINS AND DUPLICATION OF PARTS

Usually only one human child is brought forth at a birth. In about one birth out of eighty-seven, twins are produced and, much less frequently, triplets, quadruplets, or even quintuplets. Human twins are of two kinds, produced in two different ways.

1. *Fraternal* or "two-ovum" twins. Such twins are sometimes of the same and sometimes of opposite sex and do not resemble each other more than other children in the family do. Such twins are produced from two eggs liberated about the same time, each fertilized separately. They correspond to the young of such animals as rabbits and cats, which produce offspring in litters, each young one from a different egg, as shown by the number of corpora lutea in the ovaries of pregnant females.

2 *Identical* or "one-ovum" twins Such twins are of the same sex — two boys or two girls — and resemble each other so closely that none but their intimate friends can distinguish between them About one-fourth of human twins are of this kind Abundant evidence indicates that such twins come from a single egg fertilized by one sperm Though there are a few early human ova showing such twins, the exact mode of their origin has not been observed In the Texas armadillo, however, which has been carefully studied in all its stages, we have a striking example of the process This animal always produces four young at one birth, all four of the same sex The development has been traced back into the cleavage stages, where it is seen

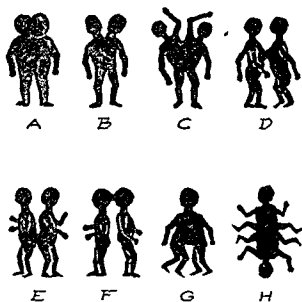


FIG 33 Outline drawings showing some of the forms of human double monsters D represents the famous Siamese twins, who lived to the age of 63 E is of the type of the Bohemian sisters, who also lived to middle life and died in 1922

clearly that all four come from one fertilized ovum The four embryos arise at a stage of development corresponding to that of a human ovum about fourteen days old by a process in which four embryos arise from one embryonic disc Probably human identical twins originate in somewhat the same way, though the indications are that the separation takes place at an earlier developmental stage than it does in the armadillo

The genetic relationship between two identical twins is the closest human relation, closer than that between parent and child or between other children from the same parents These twins have exactly the same hereditary constitution, being derived from the same egg and

the same sperm. They are of the same sex, sex being determined at the time of fertilization. The two-ovum twins, on the other hand, are no more closely related than other brothers and sisters born at different times, because each comes from a separate egg and sperm. The fact that they develop in the same uterus, at the same time, under identical environmental conditions does not change the sex or the characteristics of such individuals.

Closely related to identical twins are the various kinds of double monsters, such as the Siamese twins, where there is a connection between two more or less complete bodies. A long series of such monstrosities has been observed, involving various forms of duplicity of heads, bodies, limbs, and internal organs, all doubtless originating in different degrees of duplication or partial twinning during develop-

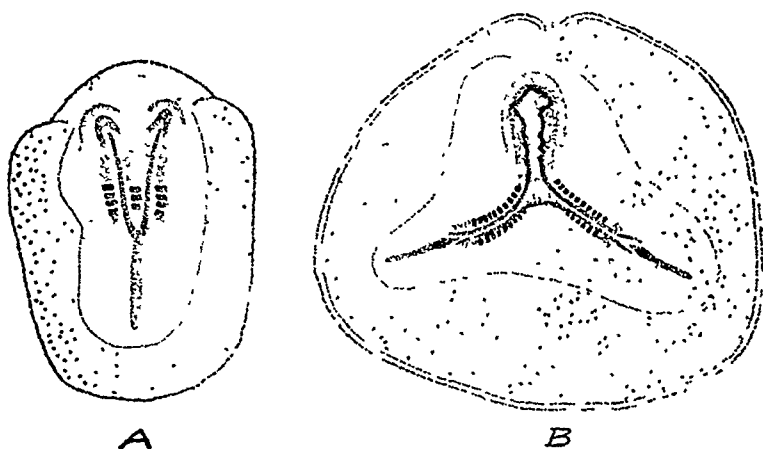


FIG. 34. Early stages of double monsters as seen in chick embryos (After Tannreuther.) *A*, Anterior duplicity. A single primitive streak with two Hensen's nodes and two notochords; two head folds and neural grooves; partial duplication of somites, the middle row being common to both embryos. *B*, Posterior duplicity. Duplication of primitive streak and partial duplication of notochord, neural tube, and somites.

ment. Figure 33 illustrates some of the kinds of human double monsters, and Fig. 34 shows early stages of two kinds of double monsters in chick embryos. The extreme of such duplication produces identical twins. Such duplicate monstrosities are by no means confined to human beings, being not uncommon in other vertebrate groups. Occasional identical twins also seemingly occur in cattle and other animals. Double monsters seldom survive more than a very short time after birth, although the Siamese twins and a few others lived to maturity.

Of interest among double monsters are some cases where one of the

individuals is well developed and the other small and ill formed, living as a parasitic mass within the other or attached to it. Teratoid tumors and cysts which develop during childhood and early adult life are believed to be of this nature.

A peculiar condition sometimes arises when there is a good-sized vascular connection in the placenta allowing free flow of blood from one twin to the other. If the heart of one twin weakens or fails to develop, the body of the heartless twin is kept alive by blood pumped by the heart of the normal twin, though such blood supply is seldom sufficient to support anything like a normal development. The result is the production of a strangely deformed being, with arms and legs deficient, or without head, or with a good-sized head and scarcely any body. In the extreme, the heartless twin is merely a formless mass with no resemblance to a human being.

F SUPERFETATION

There has long been a belief that, after pregnancy has become established, it sometimes happens that an egg from a subsequent ovulation becomes fertilized by a sperm from a later insemination, resulting in a double pregnancy with two very unequal embryos. It is probable that most, if not all, of such supposed occurrences are merely cases of twins where one has been arrested in development.

G ANOMALIES

An anomaly is a departure from the ordinary course of development which results in the production of an individual with some deformity. Only a small percentage of embryos exhibit anomalies of development. There are many kinds of anomalies, some of which result in no visible abnormality in the external form of the body, whereas others distort it in various ways. Some of the more conspicuous of such anomalies will be mentioned in the following paragraphs, but inasmuch as nearly all of them are primarily the result of anomalous development of some one system of organs, the explanations of their origins will be deferred to later chapters. Most anomalous infants die long before completing the full course of intra-uterine development and so come to premature birth.

In rare cases the body undergoes a reduced, but proportional, development which produces true dwarfs, though their real nature may not become evident until some years after birth, inasmuch as by no means all babies which are undersized when born become dwarfs. In other instances deformed dwarfs are produced whose arms and legs, though normal in thickness, do not accomplish the normal

growth in length. This condition is already present at birth, and subsequent growth does not correct it. Sometimes the arms and legs are wanting, and the hands and feet are attached directly to the body, or some or all of the limbs may be wholly wanting, the limb buds not making their appearance. The limbs of some individuals are of generally diminutive size or without fingers or toes or hands or feet. Club foot is a common congenital deformity. It is essentially an arrested development at an early fetal stage. Club hand is much less common. Sometimes the two legs are united more or less completely into one appendage.

Intra-uterine amputation of limbs is of not uncommon occurrence. There seems to be no evidence that such amputations are due to amniotic bands or other mechanical injuries, as formerly supposed. They are more probably the result of some local, congenital deficiency of growth power which becomes manifest in early fetal weeks or even earlier. Sometimes the deficiency is so great that the rudiment of a limb does not appear; in other cases a previously formed limb is actually amputated. The reverse condition, excessive growth vigor, sometimes results in the production of local gigantism in the form of a digit, for example, which is far larger than the others.

The trunk is subject to various deformities. One of them, protrusion of viscera due to failure of the body wall to be completed ventrally, gives rise to various kinds of hernias. The external genitals are subject to various malformations.

The head may be seriously deformed in a variety of ways, most conspicuous among which are various anomalies of the brain and skull, extending, in extreme cases, to entire absence of the brain and the vault of the skull. Such defects frequently extend also to the spinal cord and vertebral column (Fig. 172, p. 257). The face may be much deformed or wholly wanting, because of various failures in the development of the branchial arches. The lower jaw may be wanting or deformed, and fistulas may be present in the neck region, caused by permanent perforation of some of the branchial grooves. A common deformity is hare lip, the result of failure in the union of the median nasal process with the maxillary process on one or both sides, so that a groove is left between the nostril and the mouth. The two eyes may be variously united (cyclopia), in which case the malformed nose is usually above the eye, or the eyes may be small or wholly wanting.

CHAPTER VI

THE MEMBRANES AND THE PLACENTA

Closely associated with the child during its prenatal development and necessary for its protection and nourishment are certain structures known as membranes. There are two sets of membranes (1) the fetal membranes, which are extensions of the embryo itself, and (2) the decidual or maternal membranes, which arise as specializations of the mucosa of the uterus. The membranes are discarded at birth. The actual exchange of nutritive and waste materials between mother and unborn child is brought about through the placenta, a temporary organ which includes part of the fetal membranes and part of the decidual membranes.

A THE FETAL MEMBRANES

The beginnings of the fetal membranes were noted in Chapter IV, where it was seen that the embryo represents only a part of the developing ovum, the remainder going to produce the fetal membranes.

The Chorion

The chorion is well developed in all reptiles, birds, and mammals. It is often called the serosa, especially in reptiles and birds. Its manner of development in man is decidedly different from that in reptiles, birds, and the great majority of mammals and represents an abbreviated mode of development, though the end result is the same as in other species.

The human chorion, briefly described in Chapter IV, is formed from the trophoderm, and the underlying chorionic mesoderm (Figs 13, 14, and 15). In the development of the chorion from these structures, the chorionic mesoderm furnishes the inner layer of the chorion wall (the connective tissue) and the cores of the villi, while the spongy mass of the trophoderm (both cellular and syncytial layers) becomes thinner to form the two-layered epithelium of the chorion and its villi. This epithelium, in the first half of pregnancy, consists of an inner cellular layer (layer of Langhans) and a thin, outer, syncytial layer (Fig 46A). In the second half of pregnancy, the epithelium comes to consist of but a single syncytial layer, with here and there

a good-sized knot of syncytial tissue (Fig. 46B). As pregnancy progresses, considerable areas of epithelium degenerate to form "canalized fibrin," which stains deeply with eosin.

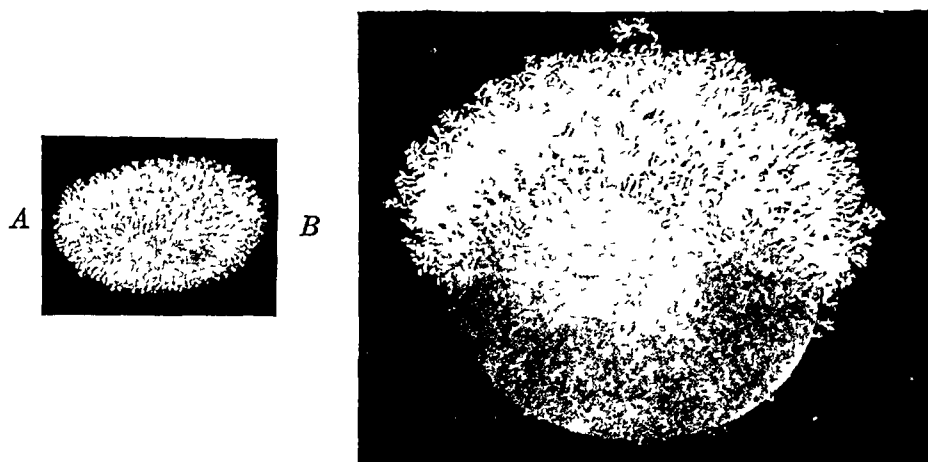


FIG. 35. Two young chorionic vesicles. *A*, age 3 weeks. *B*, age 6 weeks. (From De Lee, *Principles and Practice of Obstetrics*. W. B. Saunders Co, Philadelphia.)

The villi at first are blunt, unbranched projections (Fig. 14, p. 37), but as they grow taller, they branch more and more extensively until they become tree-like structures which form a dense growth over the

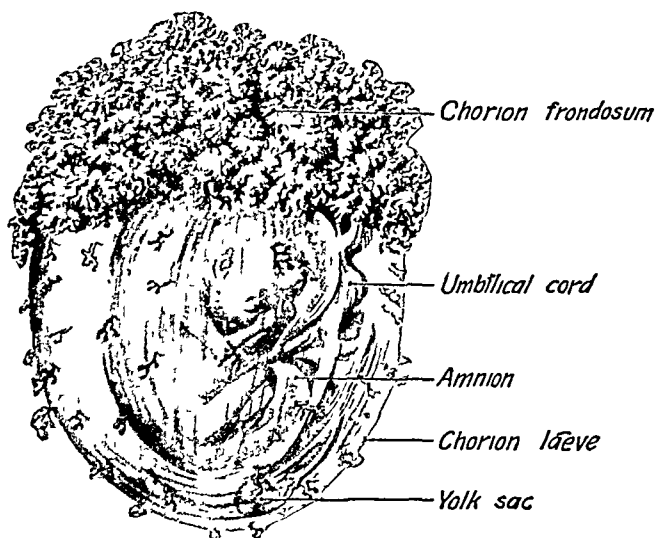


FIG. 36. Fetus 4 months old within the chorion and amnion. (From Kollmann's *Handatlas*.)

entire surface of the chorion (Fig 35). About the fourth week, however, the villi on the side toward the uterine cavity cease to grow and soon degenerate, leaving that surface smooth (Figs. 35 and 36). The

smooth side is the chorion laeve, the side on which the villi persist, the chorion frondosum. Figures 15, p 38, and 38 show in diagrammatic manner the development of the chorion.

As was pointed out in Chapter IV, the earliest primordia of developing blood vessels appear in the chorion and its villi during the third week. When circulation is established about the middle of the fourth week, the chorion is thus already richly supplied with blood vessels which connect through the umbilical cord with the vessels of the embryo (Figs 37 and 44). The chorionic villi, like the earlier syncytium of the trophoderm, are bathed with maternal blood, which is separated from the blood of the embryo only by the thin tissues surrounding the blood vessels in the villi (Figs 44 and 46). Exchange of nutritive and waste substances between fetal and maternal blood is thus made possible.

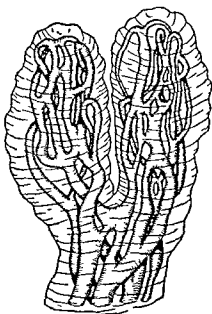


FIG 37 Tips of chorionic villi showing blood vessels (From Kollmann's *Handatlas*)

The Amnion

The amnion is a membrane of great importance in all species of reptiles, birds, and mammals and is about equally well developed in all, though its manner of development in man and a few other mammals is quite different from that in reptiles, birds, and the more primitive mammals.

The development of the human amnion begins with the formation of the amniotic cavity between the trophoderm and the embryonic ectoderm. This cavity is beginning to form in a seven and one-half-day embryo and by eleven days is of good size, as is described in Chapter IV and shown in Figs 12 and 13, p 34. The roof of this cavity is the amniotic ectoderm, which is attached to the embryonic ectoderm all the way around the margin of the germ disc. Extra-embryonic mesoderm soon forms the outer layer of the amnion (Figs 13 and 15, pp 34 and 35).

The amniotic cavity is at first broad and flattened, but as the embryonic disc folds to become the embryo, the margin of the developing amnion is carried downward and around the embryo until

it comes to be attached approximately where the yolk sac joins the embryo (Figs. 17 and 22, pp. 42 and 45). The embryo now floats freely in the amniotic cavity. In the formation of the amnion, what happens is essentially that the amniotic cavity becomes wrapped around the body of the embryo by the same folding process that forms the embryo itself.

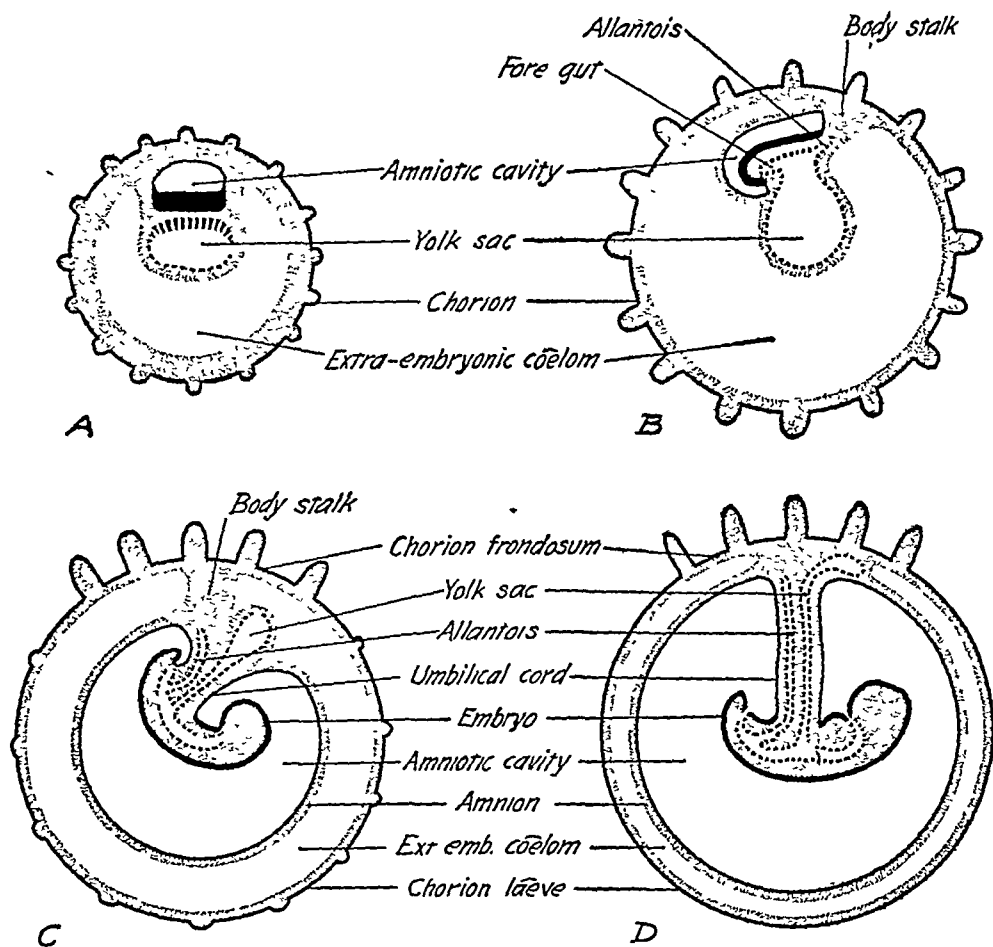


FIG. 38. Development of the fetal membranes and the umbilical cord, as seen in sections through the chorionic vesicle and its contents. *A*, about 2 weeks. *B*, about 3 weeks. *C*, about 6 weeks. *D*, about 7 weeks. The amnion and chorion are about to fuse. (Adapted from McMurich.)

After its formation the amnion expands at the expense of the extra-embryonic coelom until, about the seventh week, its outer (mesodermal) surface comes into contact with the inner (mesodermal) surface of the chorion, with which it lightly fuses (Fig. 38*D*). The amnion is without blood vessels or nerves.

The amniotic fluid increases in amount as pregnancy progresses. It varies greatly in amount, but perhaps 1000 cc. at full term is about

average Its nature and source have been studied extensively, but knowledge is still incomplete It is a clear fluid with a salt concentration lower than that of either fetal or maternal blood It contains increasing amounts of urea and uric acid, which indicates that it is in part a product of the fetal kidneys It is also suspected, however, that it may be produced partly by the epithelium of the amnion and that on the surface of the fetus It is known that the fetus swallows large amounts of the amniotic fluid

During the months previous to birth, the amnion and the amniotic fluid serve as a cushion which protects the fetus from external injury and at the same time allows it freedom of motion The fluid also tends to prevent deformities caused by the adhesion of surrounding structures to the embryo, a condition which results when the amount of fluid is scant During labor the amniotic fluid assists by equalizing the pressure within the uterus At birth a portion of the amnion and surrounding chorion containing the amniotic fluid usually precedes the head of the fetus through the cervix of the uterus and thus assists in dilating the passage The bag usually ruptures a little later in labor, liberating the "waters" Very rarely the head of the child is born with the unbroken amnion still surrounding it as a veil, a condition which has long been superstitiously considered an omen of good luck.

The Yolk Sac

The origin of the yolk sac is described in Chapter IV and illustrated in Figs 12 to 15, pp 34 to 38, and Fig 38 It is a small vesicle lined with entoderm When the extra-embryonic coelom is formed by separation of extra-embryonic mesoderm into somatic (chorionic) and splanchnic layers, the splanchnic layer becomes the mesodermal layer of the yolk sac The yolk sac is an organ of great importance in the embryonic stages of fishes, where it is the only fetal membrane and contains the yolk, the food supply of the embryo In reptiles and birds, also, it contains much stored food In mammals it cannot be of more than temporary nutritive importance, since it contains no yolk It still serves an important developmental purpose, however, in that nearly all the epithelium of the alimentary tract develops from its entoderm, and the earliest blood cells from its mesoderm

When the embryo is formed by folding of the embryonic disc, the yolk sac remains connected to the embryo by the yolk stalk (Figs 17 and 21, pp 42 and 44, and Fig 39) and its cavity is continuous with that of the embryonic digestive canal The sac persists as a small vesicle until birth, usually lying between the chorion and the amnion

(Figs. 39 and 43), but the stalk commonly degenerates by about the second month. The relationships between yolk sac, embryo, and other structures are shown in the series of diagrams of Fig. 38.

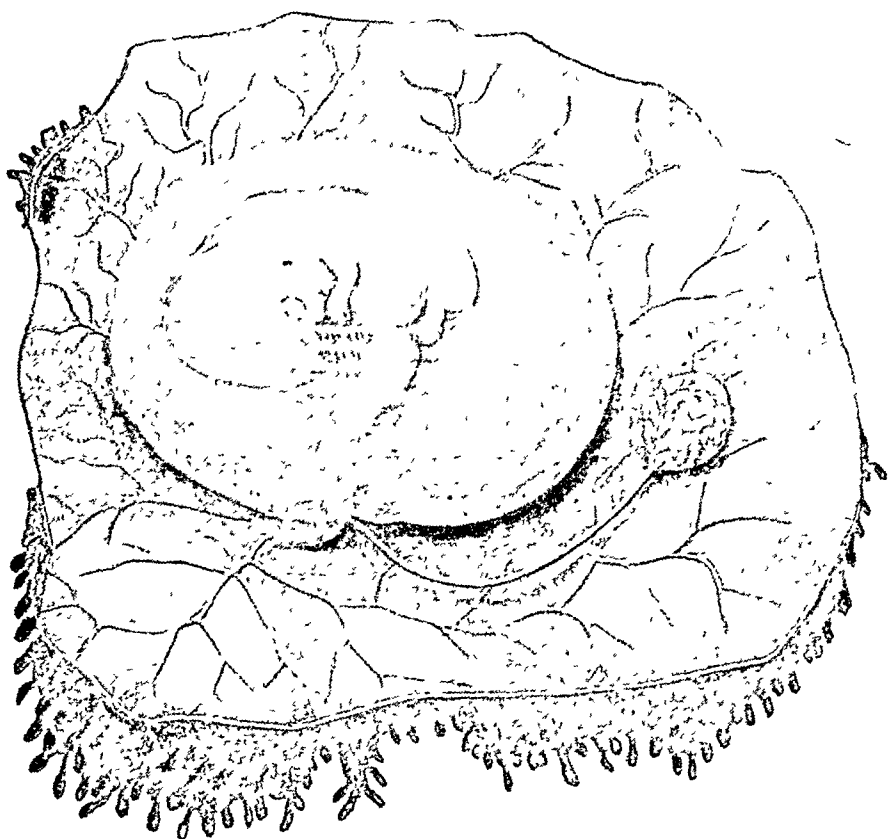


FIG. 39. Human embryo 20 mm. long (7 weeks), enclosed by the amnion. The chorion has been opened and partly cut away. Shows the following: embryo, umbilical cord, amnion, inside surface of chorion with umbilical vessels, chorionic villi, yolk stalk, yolk sac with vitelline vessels.

The Allantois

In birds and reptiles the allantois has the form of a large sac and is a membrane of great importance, being the embryonic respiratory organ, and serving also as a reservoir for the secretion of the embryonic kidney. It is well developed in some mammals also, where it forms the fetal part of the placenta, but in man and a few other mammals it is only a small tubular remnant embedded in the substance of the umbilical cord and is of no apparent importance. Its blood vessels, however, known as the umbilical vessels, extend far beyond it and become the vessels of the chorion frondosum, through which the nutrition of the embryo is received.

The human allantois arises as an outgrowth from the entodermal cavity, even before the embryo has been formed. It is present as early

as the seventeenth day (Figs 15 and 16, pp 38 and 41, and Fig 38) It pushes out into the mesoderm of the body stalk and occupies such a position that, when the embryonic hind gut forms, the allantois is connected to its ventral side (Fig 38) It usually degenerates wholly by the middle of pregnancy

The four fetal membranes first attained high development in animals which develop from eggs containing much stored food They are thus well adapted to meet the nutritive needs of the embryos of reptiles and birds In mammals, whose eggs have little or no yolk, the membranes serve the same purpose by establishing intimate contact with the mucosa of the uterus, from which they draw nutriment for the embryo In more primitive mammals the condition of the membranes differs but little from that in reptiles and birds, but in higher species considerable modification has taken place Probably the most advanced type is found in human beings, where not only is the developing ovum brought into very intimate relation with the maternal blood, but also there are certain abbreviations of development

B THE UMBILICAL CORD

The umbilical cord is the structure by which the fetus is attached to the chorion frondosum Its mode of formation is shown in Fig 38, also in Figs 21 to 24, pp 44 to 46 It develops as follows When the embryo begins to form from the embryonic disc, its posterior end is joined to the chorion by a short mesodermal connection, the body stalk (Figs 15, p 38, and 38B), which may be regarded as the beginning of the umbilical cord While embryo formation is in progress, the connection of the body stalk shifts from the posterior end of the embryo to its mid-ventral surface At the same time the amniotic cavity surrounds the embryo and the body stalk more and more completely During this process the body stalk, the yolk stalk, and the allantois become bound together to form a single structure, the umbilical cord, whose superficial layer is formed by the ectodermal epithelium of a portion of the amnion (Fig 38)

The umbilical cord becomes definitely formed by the middle of the second month, well within the embryonic period It attains an average length of 55 cm, sufficient to allow the child to be born while the placenta is still attached within the uterus

The vessels carrying blood between the embryo and the chorion frondosum (two umbilical arteries and one umbilical vein) run through the umbilical cord, but they develop before the umbilical cord is fully formed, at that time running through the body stalk

(Figs. 39 and 43), but the stalk commonly degenerates by about the second month. The relationships between yolk sac, embryo, and other structures are shown in the series of diagrams of Fig. 38.

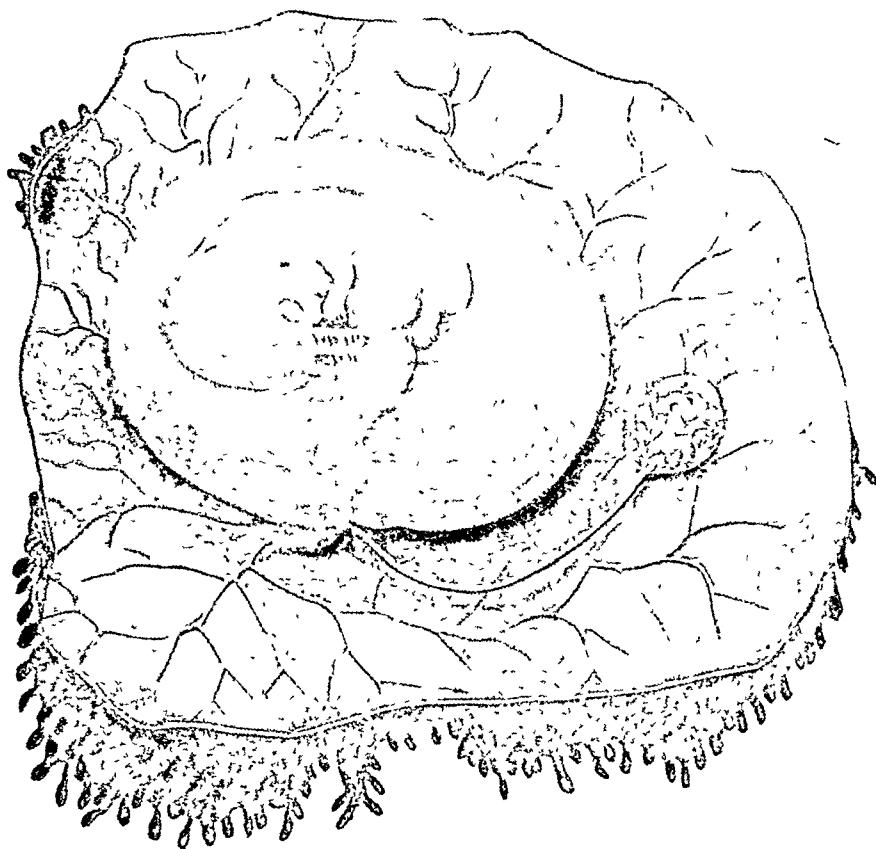


FIG. 39. Human embryo 20 mm. long (7 weeks), enclosed by the amnion. The chorion has been opened and partly cut away. Shows the following: embryo, umbilical cord, amnion, inside surface of chorion with umbilical vessels, chorionic villi, yolk stalk, yolk sac with vitelline vessels.

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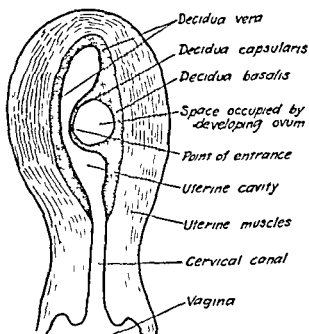


FIG 40 Diagram of section through the gravid uterus at an early stage, showing the decidua membranes

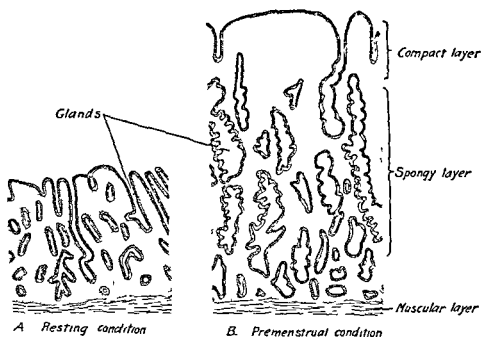


FIG 41 Diagrammatic sections through the mucosa of the uterus *A*, resting condition *B*, premenstrual condition Represents also the early decidua mucosa of pregnancy

(Fig. 117, p. 165). Thus by the middle of the fourth week there is circulation of blood between the embryo and the chorion by way of the body stalk.

The umbilical cord is covered with epithelium derived from amniotic ectoderm, enclosing a mass of mucous tissue (Wharton's jelly) developed from mesoderm. Embedded in the mucous tissue are the umbilical arteries and vein. In the earlier months of pregnancy the entodermal tubes of the yolk stalk and allantois are also present, but these disappear well before the end of pregnancy. Nerves have not been demonstrated in the blood vessels or other tissues of the umbilical cord or chorion, even though they are clearly seen in the portion of the umbilical vessels within the abdomen.

C. THE DECIDUAL MEMBRANES

The uterus responds to pregnancy in the following definite manner. (1) It grows greatly in size, due to hypertrophy of the muscular coats. This is actual growth, not stretching due to pressure from the growing fetus. The increase in size is more than enough to contain the enlarging contents; the wall grows to three times its former thickness, and the mass of muscle increases twenty-four-fold. The full-term uterus has a capacity of 4000 to 5000 cc. (2) The blood supply increases sufficiently to supply the fetus. (3) The decidual membranes develop.

In man and other higher mammals, where the union between the chorion and uterus is very intimate, the mucosa of the pregnant uterus undergoes pronounced changes, producing structures known as decidual membranes or deciduae. So intimate is the fusion between the human decidua and the chorion that at birth the superficial part of the decidua comes away, along with the fetal membranes. The decidual membranes develop in the following manner.

When the ovum becomes implanted in the uterine mucosa, the hole through which it enters becomes closed with a plug of clotted tissue fluid, which is soon replaced by growing tissues, so that the ovum is wholly surrounded by the tissues of the uterine mucosa. As the ovum grows, the space in which it lies enlarges correspondingly, and the part of the mucosa between it and the uterine cavity is pushed outward, making a bulging into the cavity (Fig. 40). There can now be distinguished the three decidual membranes: (1) the decidua capsularis — the part of the mucosa arching over the ovum, between it and the uterine cavity; (2) the decidua basalis — the part underlying the ovum, between it and the muscular layers; and (3) the decidua vera — the remainder of the mucosa, including the parts not

its vascular villi. Accordingly, it undergoes progressive development in connection with the growing needs of the embryo and is more fully treated in the discussion of the placenta.

In all the deciduae, some of the connective tissue cells become converted into the large decidual cells characteristic of pregnancy. They are often multinucleate and may be as large as 100 microns (Fig 42). As the uterus becomes enlarged during the progress of pregnancy, the spongy layer of the decidua vera and decidua basalis is made more pronounced by the stretching of the layer, and in consequence the glands become large, horizontal spaces, lined with flattened epithelium. Thus develops the zone of weakness where the separation takes place when the deciduae are expelled after the birth of the infant (Fig 43).

D THE PLACENTA

The placenta is a temporary organ formed from parts of two persons, the mother and the unborn young.

The two parts of the placenta are the *decidua basalis* (the maternal part) and the *chorion frondosum* (the fetal part). Between these two parts is a space or sinus, the intervillous space, into which maternal blood is discharged from the uterine arteries which were eroded during the implantation of the ovum and its subsequent growth (Figs 43 and 44). This blood is constantly changed as it escapes from the uterine arteries and returns to the uterine veins. It is the general belief, however, that this flow of blood through the sinus is sluggish, although it is sufficient to meet the nutritive needs of the fetus. Into this reservoir of maternal blood dip the richly branched villi of the chorion frondosum. Within the villi are the capillaries from the umbilical vessels which reach the chorion from the fetus through the umbilical cord (Figs 37 and 44).

The circulation of the placenta is accordingly a double one, including two distinct parts: (1) the *fetal part* in the chorionic villi and (2) the *maternal part* in the intervillous space.

Exchange of materials takes place in the following way. Food and oxygen, carried by the maternal blood, are absorbed through the surface of the villi into the fetal blood, whereas carbon dioxide and other wastes of metabolism of the fetus pass from the fetal blood within the villi into the maternal blood which bathes them. It should be noted in this relation that the fetus has its own independent circulation and that, contrary to popular belief, the blood of the mother does not flow through the vessels of the unborn child. The two blood

in contact with the ovum. The decidua basalis is in contact with the chorion frondosum; the decidua capsularis with the chorion l  ve.

The decidual membranes bear a decided resemblance to the pre-gravid mucosa from which they develop. In the pregravid condition the blood supply of the mucosa is much increased and the glands enlarged. The enlargement of the glands is more marked in the deeper layers than in the superficial, a fact which results in the formation of the compact and spongy layers (Fig. 41).

As previously pointed out, the fertilized ovum reaches the uterus during the pregravid stage, and its presence prevents the customary menstrual flow with its loss of tissue and blood. Instead of the menstrual flow, further development of the decidual membranes takes place.

The Decidua Vera

The decidua vera is the part of the uterine mucosa which undergoes the least change during pregnancy. It includes the entire thickness of

the endometrium, and its structure is just a further development of the pregravid condition. Its superficial epithelium disappears early in pregnancy, and during the latter months the entire layer becomes thinner and less vascular.

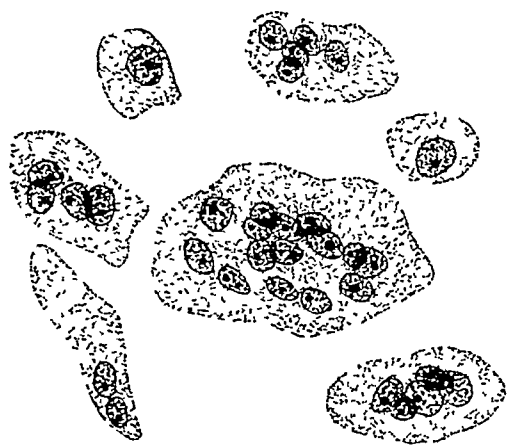


FIG. 42. Decidual cells drawn from a human afterbirth.

The Decidua Capsularis

The decidua capsularis includes only the superficial part of the endometrium. It is at first covered with epithelium

and contains blood vessels and the upper portions of the glands. As it is pushed outward by the growing chorion l  ve, it becomes reduced to a thin membrane, which, about the fifth month, reaches the decidua vera and fuses with it, thus obliterating the lumen of the uterus. Figure 43 shows diagrammatically a stage where the fusion is just about to take place.

The Decidua Basalis

The decidua basalis has the same structure as the decidua vera except that it lacks the superficial stratum (Fig. 40). It is the part of the endometrium under the influence of the chorion frondosum with

Just inside the closing ring the villi are poorly developed, leaving a rather open part known as the marginal sinus. From the decidua basalis there extend into the maternal blood sinus a number of wall-like growths, the placental septa (Figs 43 and 44), which extend

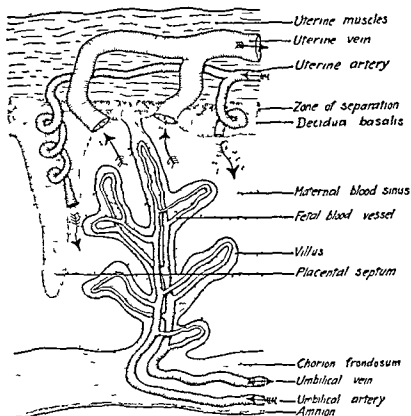


FIG 44 Diagrammatic section through placenta, showing especially the two circulations, maternal and fetal (Adapted from Kollmann's *Handatlas*)

among the villi, separating them into groups known as cotyledons. The septa do not unite with the chorion frondosum, but some of the anchoring villi are attached to them. In the earlier stages of pregnancy the syncytial epithelium of the chorion spreads over the eroded surface of the decidua basalis from the ends of the anchoring villi, so that for a time the blood sinus is lined throughout by chorionic epithelium. The surface of the placenta to which the umbilical cord attaches is covered with a portion of the amnion (Figs 43 and 44), which at the placental margin extends outward in contact with the chorion laeve.

The placenta at full term has the form of a disc somewhat thinned, at the margin. It measures 16 to 20 cm. in diameter and about 3.5 cm. in thickness. It weighs about 500 grams. In a vertical section through the placenta it is seen that the decidua basalis and the chorionic

streams come only close enough together so that an exchange of some substances may take place between them.

The structure of the placenta should now be examined in greater detail. The fetal and maternal parts of the placenta are held together

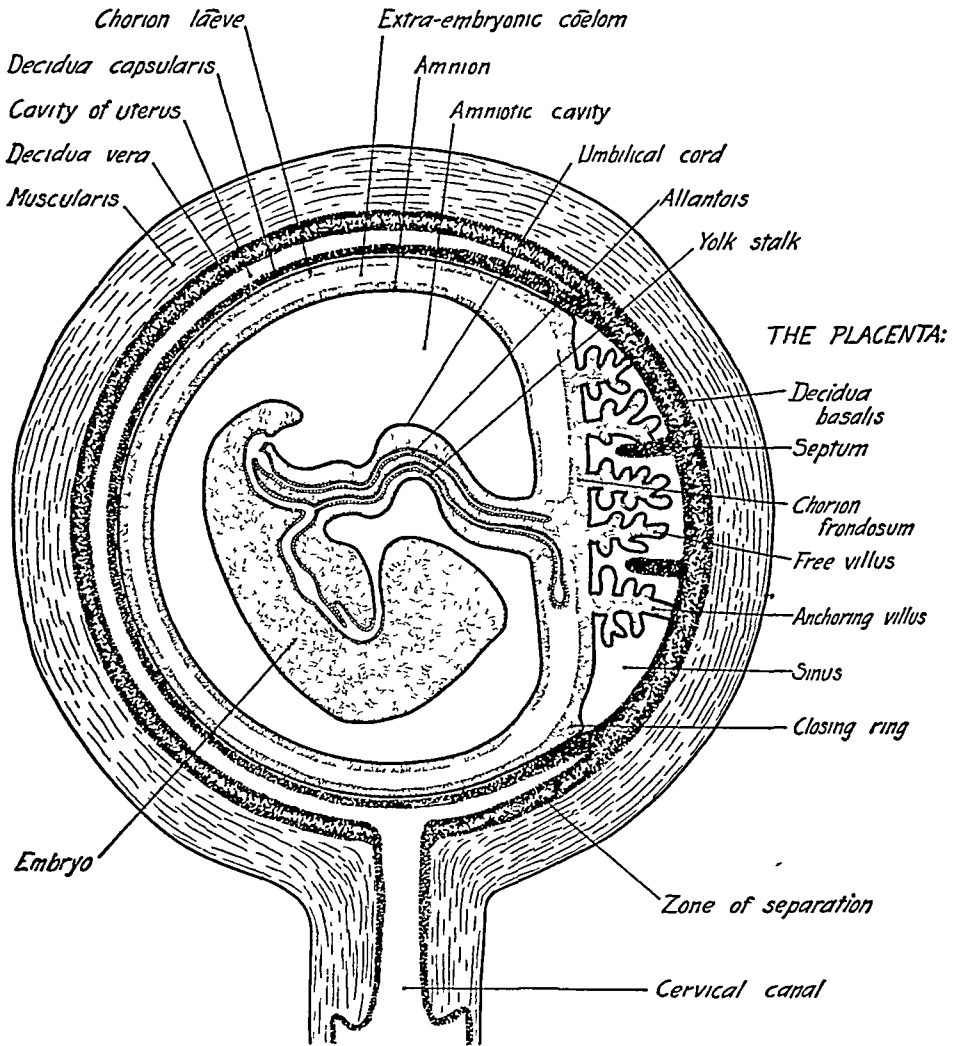


FIG. 43. Diagram of section through the pregnant uterus and its contents, as at about the seventh week.

in two ways: (1) by anchoring villi and (2) by the closing ring or plate. The anchoring villi are those whose distal ends attach to the plate. The free villi float freely in the maternal blood within the sinus (Figs. 43 and 44). At the margin of the placenta, the decidua and the chorion are firmly united, the union being known as the closing ring or plate. This plate serves both to unite the two parts of the placenta and to prevent the escape of blood from the sinus at the margin (Fig. 43).

both the placenta and the membranes are expelled. The placenta, the membranes, and the umbilical cord constitute the afterbirth (Fig 47)

The separation of the afterbirth strips a layer from the entire inner surface of the endometrium. This process is accompanied by the tearing of many maternal blood vessels, including the large ones of the placental area (Fig 44), which would cause fatal hemorrhage if the continued contraction of the uterine musculature did not reduce the organ to a compact mass, thereby mechanically preventing excessive bleeding.

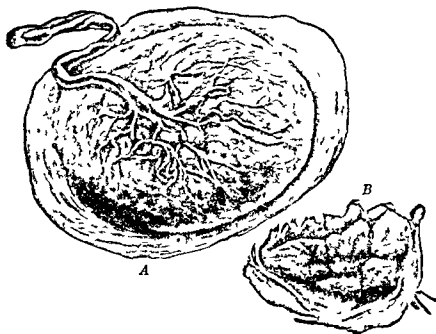


FIG 47 Mature placenta as seen in human afterbirth. A, entire organ showing fetal surface with fetal blood vessels converging at the umbilical cord and the membranes attached at the margin. B, part of the maternal surface, showing cotyledons separated by grooves. (From Heisler's *Text-book of Embryology*, W. B. Saunders Co., Philadelphia.)

After the separation of the afterbirth the uterine mucosa is wholly devoid of surface epithelium. There remain, however, the basal portions of the glands below the spongy layer, from which the entire epithelial portion of the uterus regenerates. The tunica propria is restored by growth of the fibrous portion of the decidual layer. The separation of the decidual membranes in the afterbirth and the ensuing regeneration of the endometrium are comparable to a delayed menstruation and the subsequent healing process (Fig 32, p 52).

plate are but thin membranes, and that by far the greater part of the placenta is made up of the sinus containing the villi (Fig. 45). It has been computed that, in an entire horizontal section through a placenta, over 700,000 villi would be cut and that the total surface of the villi bathed by the maternal blood may be as much as 12 square meters.

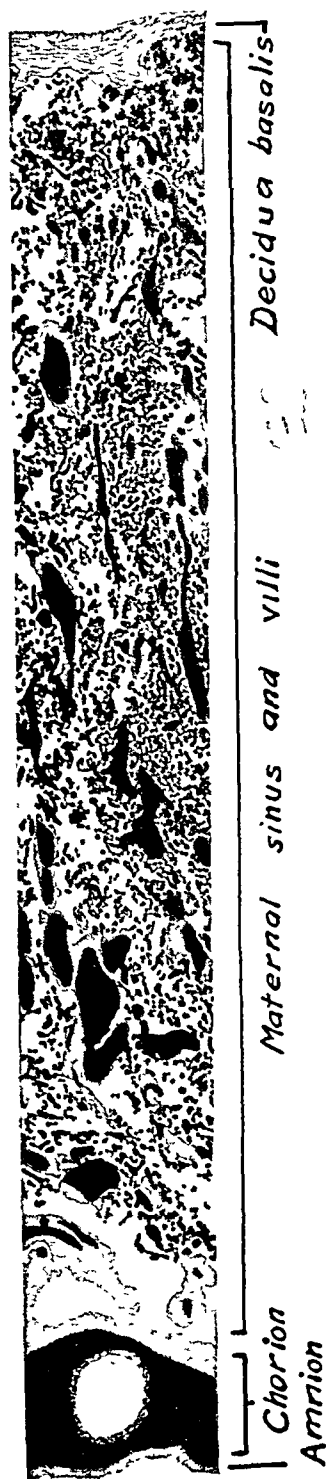


FIG. 45. Section through human afterbirth.

E. THE AFTERBIRTH

During the birth of the baby the amnion and the chorion l ave rupture, allowing the amniotic fluid and the child to escape through the cervical canal of the uterus, but the membranes are not otherwise damaged and for a short time retain their attachment to the uterine wall. Soon, however, usually in a few minutes, the contractions of the uterus separate the placenta at the spongy layer, and before long

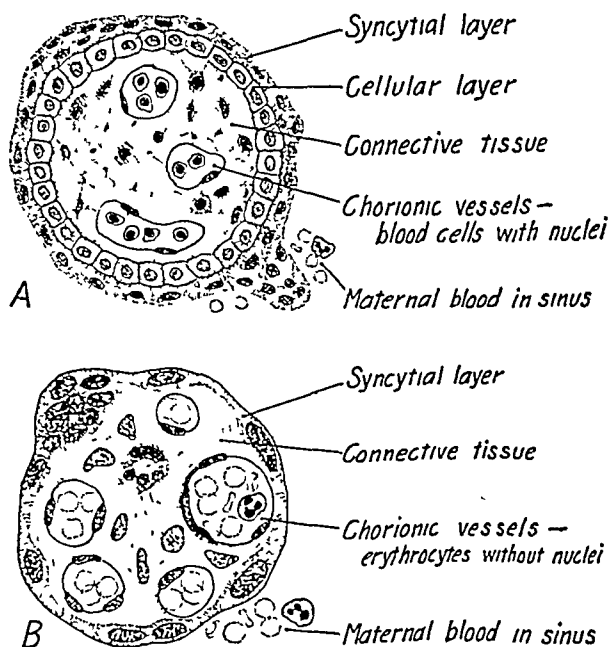


FIG. 46. Sections through human chorionic villi, highly magnified to show tissue structure. A, in early pregnancy (6 weeks). B, at full term.

layers (two chorions and two amnions), whereas that between one-ovum twins has but two layers (two amnions) or, rarely, none at all

The Position of the Placenta The placenta forms wherever the fertilized ovum becomes attached. This is most frequently on the posterior wall of the uterus, less frequently on the anterior wall and other positions. Rarely, the placenta forms so close to the cervical canal that it partially or wholly covers the internal orifice, in which case it is known as placenta prævia. This is a serious matter, because at the cervical canal the decidua basalis is wanting, a condition which allows blood from the maternal sinus to escape through the cervical canal.

Extra-Uterine Pregnancy In rare instances the fertilized ovum fails to reach the uterus and becomes implanted in the Fallopian tube, or, much less frequently, in the ovary. In these locations development

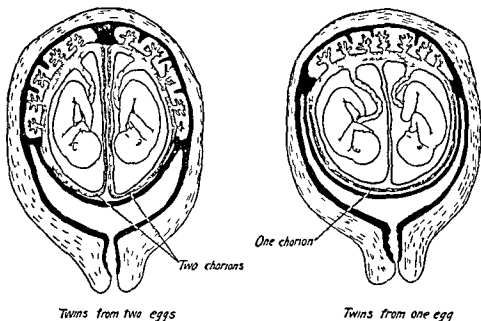
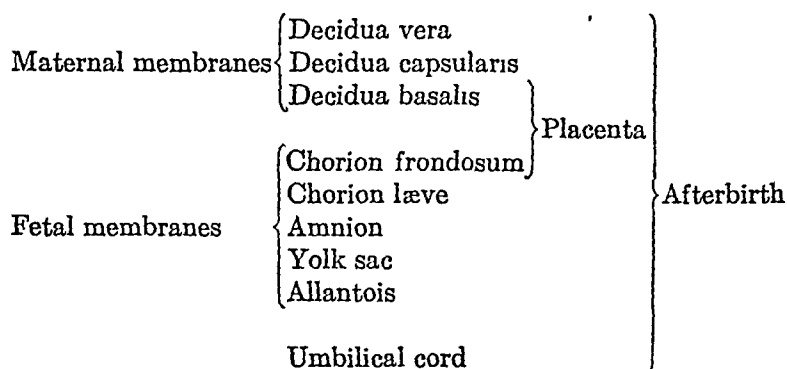


FIG 48 Twin placentas of two kinds (Adapted from Kollmann's *Handatlas*)

sometimes progresses considerably, but more frequently such pregnancies terminate in the early months. Sometimes a pregnancy is observed in the abdominal cavity with placental attachment to some part of the peritoneum, but the consensus of opinion now is that such locations are secondary, resulting from rupture of a tubal pregnancy. Extra-uterine pregnancies (also called ectopic pregnancies), in addition to their great clinical importance, present points of scientific interest.

In the extra-uterine positions a fairly typical placenta develops

The following outline may be useful in summarizing the relation between the placenta and the various associated structures.



F. GENERAL NOTES

Degrees of Placental Union. All mammals above the egg-laying monotremes have placentas, but the degree of development and the intimacy of the placental union vary greatly. The ascending series with the names of the different types of placental structure follows in brief form. (1) **Temporary, imperfect placenta** (marsupials, such as opossum and kangaroo). Epithelium of chorion makes short-duration contact with epithelium of endometrium. (2) **Epithelio-chorial placenta** (non-ruminant ungulates, such as horse and pig). Chorionic villi occupy pits in endometrium. Epithelium persists on both villi and endometrium. (3) **Syndesmo-chorial placenta** (ruminants, such as sheep and cattle). Epithelium of endometrium destroyed in local areas. Epithelium of villi in contact with connective tissue of endometrium. (4) **Endothelio-chorial placenta** (carnivores, such as dog and cat). Epithelium of villi in contact with endothelium of endometrial blood vessels. (5) **Hemo-chorial placenta** (man, monkeys, and lower rodents, such as pocket gopher). Endometrial blood vessels opened, forming sinus of maternal blood which bathes the epithelium of the villi. (6) **Hemo-endothelial placenta** (higher rodents, such as rat, guinea pig, and rabbit). Epithelium of villi destroyed. Endothelium of chorionic capillaries bathed by maternal blood in sinus.

The Membranes of Twins. The membranes are of interest also in connection with the two kinds of twins described in Chapter V. For two-ovum twins there are two complete placentas, which may be close together or separated to varying extents, and also two distinct chorions and amnions (Fig. 48). For one-ovum twins there is one placenta and one chorion, though there are usually two distinct amnions. The partition between two-ovum twins consists of four

CHAPTER VII

THE EARLY HISTORY OF THE MESODERM

In Chapter V it was pointed out that the embryo is formed from the three layers of the flat embryonic disc, which become rolled into a tube with ectoderm covering the outside, entoderm lining the cavity within, and mesoderm between these two layers (Fig 17, p 42) The external appearance of the primitive groove, neural groove, and somites has also been described. It is now in order to inquire into the internal changes during the early stages of the embryo.

A. THE EARLIEST MESODERM

In Chapter IV it was seen that in the developing human ovum of eleven days a considerable amount of extra-embryonic mesoderm already has formed, occupying the cavity of the blastocyst inside the trophoderm (Fig 13, p 35). This mesoderm is derived from the trophoderm and, as already pointed out, makes no contribution to the formation of the embryo proper. It was also pointed out that at the beginning of the third week there is no mesoderm between the ectoderm of the germ disc and the underlying entoderm, and in a general way the first formation of embryonic mesoderm was described in connection with the primitive streak. There are thus two distinct formations of mesoderm. The first arises very early and participates in the development of the fetal membranes, the second appears later by an independent process and gives rise to the mesodermal tissues of the embryo proper.

B. THE PRIMITIVE STREAK

At the fifteenth or sixteenth day the primitive streak makes its first appearance. In the Mäcker embryo and others of seventeen or eighteen days it is well developed, being seen in the posterior end of the embryonic disc as a faint longitudinal line which is marked superficially by the primitive groove (Fig 16, p 41). The primitive streak is a narrow region where the ectoderm is considerably thickened on its lower surface, and from the two edges of this thickening, a sheet of cells grows out laterally between ectoderm and entoderm. These two sheets of tissue are the embryonic mesoderm (Fig 49). These

by the usual interaction of the chorion with the surrounding tissues, whether of ovary or Fallopian tube. It is of interest that in extra-uterine pregnancies the uterus undergoes hypertrophy as if it were carrying the developing ovum, enlarging to about the size of a three-month pregnancy. In addition, the uterine mucosa develops into a well-established decidua, resembling the decidua vera. The death of a fetus in an extra-uterine position is often followed by spurious labor and the extrusion of the decidua. Thus the uterus behaves somewhat as if it actually contained a developing ovum, this reaction doubtless being due to hormones produced by the ovum, to which the body of the pregnant woman responds in characteristic manner.

solid rod of cells known as the notochord. In its subsequent growth the notochord is independent of the entoderm and continues to elongate by growth from the primitive node and also by interstitial growth along its length, thus keeping pace with the growth of the embryo. It extends nearly, but not quite, to the anterior end of the embryo. The opening of the notochordal canal in the primitive node persists for a short time, forming between the amniotic cavity and the yolk sac a direct connection which is known as the neurenteric canal (Figs 15 and 18, pp 38 and 42).

The notochord is a part of the mesoderm. It is composed of a unique tissue known as notochordal tissue, which is perhaps more like cartilage than any other tissue. It forms the primitive spinal column of the embryo, but during later development it is almost wholly replaced by the bony vertebral column.

D THE EARLY DIFFERENTIATION OF THE MESODERM

At the level of the primitive streak, where the mesoderm is in process of formation, the lateral sheets are united with the ectoderm in the mid line (Figs 49 and 50). But as these two sheets grow laterad

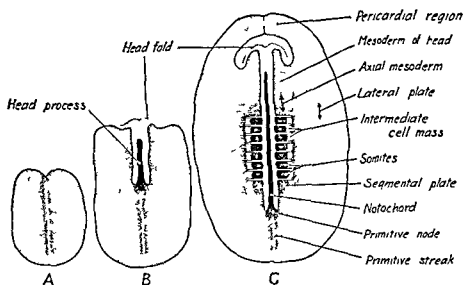


FIG 50 Diagrams showing general plan of mesoderm at three early stages
Other parts of embryo omitted

and cephalad, their medial margins in front of the primitive node are not connected with each other nor with any other structure but are separated by the notochord and the neural tube (Fig 52B). Later,

mesodermal sheets spread laterad and cephalad, forming wing-like expansions which continue to grow during the period of embryo formation and at the same time undergo differentiation into various mesodermal structures which form during these early weeks. The primitive streak continues to function as a source of mesoderm until the embryo has definitely taken form, its last manifestation being in the tail bud, from which the posterior end of the embryo is formed. It should be noted that, though the origin of the mesoderm is by cell

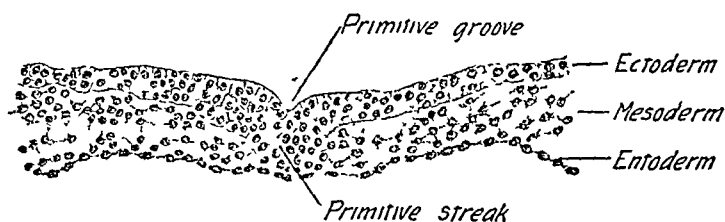


FIG. 49. Cross-section through Mateer embryo, showing the primitive streak. (Redrawn from Streeter in *Cont. to Emb.*, Carnegie Inst., Washington.)

proliferation in the primitive streak, its subsequent growth is accomplished by cell divisions scattered throughout the mesoderm. Figures 16 to 21, pp. 41 to 44, illustrate the decrease in actual and relative length of the primitive streak until its final disappearance. In embryos like that in Fig. 21, p. 44, it is still represented in the tail bud.

The primitive streak is indeed a primitive region of the embryo, a region where proliferation of undifferentiated cells is going on. It has been compared to the growing tip of a plant root, a germinal region of primitive tissue which moves steadily caudad, leaving in its wake the more mature tissues which are produced by its activity.

C. THE NOTOCHORD

At the anterior end of the primitive streak there is a small area where all three germ layers are fused together, known as the **primitive node** (Hensen's node). It is essentially a part of the primitive streak, though it takes no part in the formation of the mesodermal sheets. It does, however, produce the **notochord**, a rod of tissue lying in the mid line between ectoderm and entoderm. In the development of the human notochord there first grows forward from the primitive node a hollow cylinder, the **head process**; its lumen, the **notochordal canal**, opens through the primitive node. The head process fuses with the underlying entoderm, but its lower wall, which is fused with the entoderm, soon breaks down, and its roof rounds up to become the

formed not far from the primitive node, and the later ones in succession between the earlier ones and the primitive node. Those closest to the node are the youngest. Continued growth of axial mesoderm just above the primitive node furnishes the material for the newest somites. The first somites form at the beginning of the fourth week. The full number, probably forty-one pairs, is attained in embryos of about 7 mm (early in the sixth week), a period of about two weeks being covered in their formation. The somites give rise to the vertebrae, the ribs, and the muscles of the neck and trunk.

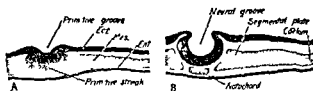


FIG 52 Two sections through a chick embryo 24 hours old A, through primitive streak B, through segmental plate

The axial mesoderm of the head remains largely unsegmented, only three or four imperfectly developed somites forming in the occipital region of the head. The bones of the cranium are developed from unsegmented axial mesoderm.

The Intermediate Cell Mass The thinner zone of mesoderm between the somites and the lateral plate is the intermediate cell mass or nephrotome, the latter name being applied because from this zone develop the excretory organs (Figs 50 and 53A). The nephrotome is treated in Chapter XVII.

The Lateral Plates The lateral plates attain considerable extent. They extend far cephalad and rather early unite in the mid line in front of the head fold. From this anterior region the pericardium originates. The lateral plates soon split into somatic and splanchnic layers, between which is the coelom or body cavity (Fig 53A). For a time this embryonic part of the coelom becomes continuous with the large extra-embryonic coelom, which develops earlier (Figs 14 and 84, pp 37 and 126). The somatic layer, together with the ectoderm, forms the somatopleure, which develops into the body wall. The splanchnic layer and the entoderm in similar manner form the splanchnopleure, which becomes the wall of the alimentary canal. The coelom later becomes subdivided into the pericardial, pleural, and peritoneal cavities.

The lateral plates do not extend into the head fold, except that

however, the two halves become united by continued growth. At their lateral margins these sheets are, almost from the first, in continuity with the extra-embryonic mesoderm which forms earlier than the embryonic mesoderm. This relation is shown in Figs. 51 and 84, p. 126, but not in Fig. 50.

At the level of the primitive streak the newly formed mesoderm is without evident regional differentiation, but the older portion of the mesoderm, cephalad of the primitive node, undergoes progressive differentiation. Here three longitudinal regions soon become recognizable: (1) the axial mesoderm, in which the mesodermal somites

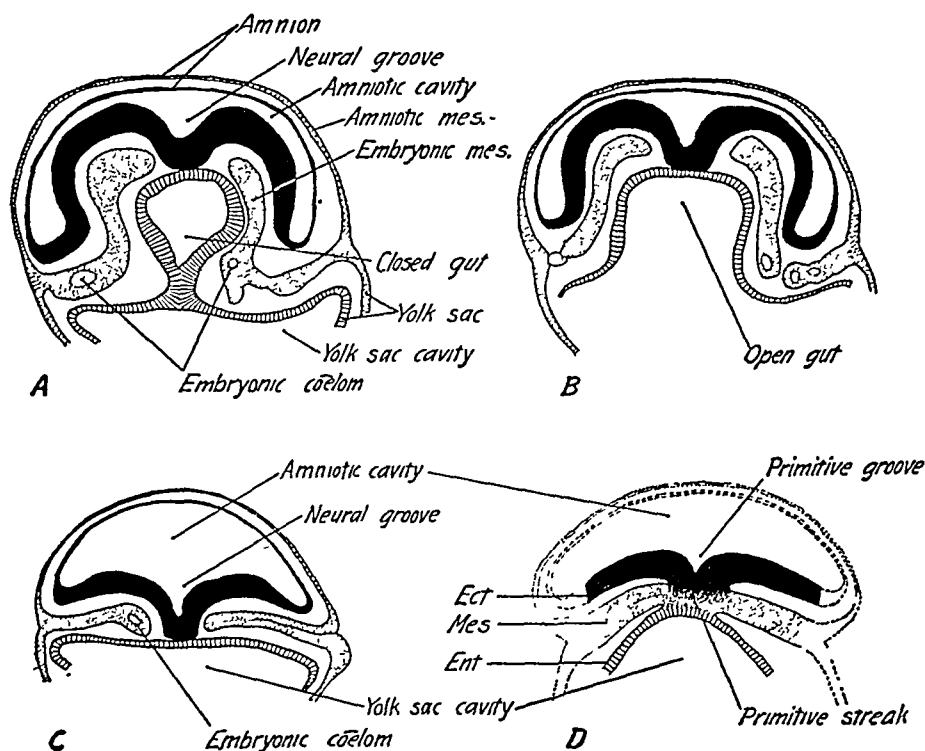


FIG. 51. Diagrammatic pictures of cross-sections through the Spee embryo *Gle*, at four different levels *A*, through closed fore gut. *B*, through open fore gut. *C*, through region at about middle of embryo. *D*, through primitive streak. (Adapted from Keibel and Elze's *Normentafeln*.)

form; (2) the intermediate mesoderm (intermediate cell mass or nephrotome); and (3) the lateral mesoderm (lateral plates) (Fig. 50). These three regions are well differentiated in the neck and body regions but only partially in the head.

The Somites. The axial mesoderm begins early to segment into successive pairs of blocks, the somites. The earliest somites are

posed of anastomosing cells of stellate form (Fig 54) From mesenchyme develop all the supporting tissues

Differentiation of the Somites Each somite at first contains a closed cavity, but this is soon filled with loose tissue by migration of cells from the wall of the somite (Fig 53A) Further differentiation of the somite into three parts, sclerotome, dermatome, and myotome, quickly follows

The sclerotome is formed from the central core and the wall of the somite toward the notochord The cells of these parts of the somites become mesenchymal and migrate toward the notochord and neural tube, about which they mass themselves (Fig 53B and C) From the sclerotome develop the vertebrae and ribs The short remaining part of the mesial wall of the somite doubles back sharply just

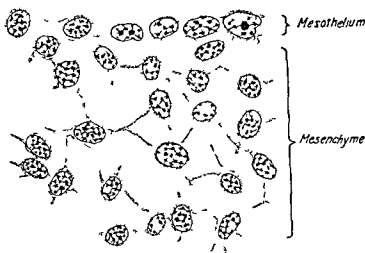


FIG 54 The two early mesodermal tissues, mesothelium and mesenchyme, as seen in a pig embryo 5 mm long

inside the outer wall and grows ventrad just inside it, thus forming a two-layered structure known as the dermo-myotome (Fig 53B and C), the outer layer being the dermatome and the inner the myotome The myotome gives rise to the muscles of the trunk The dermatome has been thought to give rise to the fibrous layers of the skin and probably does so in some vertebrates, but it is now generally believed that in mammals it unites with the myotome to form muscles

The Mesoderm of the Head As previously pointed out, the mesoderm of the head does not undergo differentiation into somites, intermediate cell mass, and lateral plate, nor does the coelom extend into it Instead, the mesoderm in this region has the form of a loose mass of mesenchyme This is, in part, a forward extension of the

splanchnic mesoderm in the pharyngeal region forms the muscles and bones which develop in the branchial arches. These muscles and bones play an important part in the development of the head, as described in Chapters VIII and IX. Nor does the coelomic cavity extend into the head, except that the pericardial cavity is a part of the coelom that lies for a time adjacent to the pharynx, until it and the heart are carried into the thorax (Fig. 117, p. 165).

Students of the embryology of reptiles and birds will remember that in them the somatopleure and the splanchnopleure undergo folding to form the fetal membranes. The fetal membranes of most mammals are derived in that same fashion, but in man and a few other mammals they develop in the abridged manner described in Chapters IV and VI. The end results are the same by both methods.

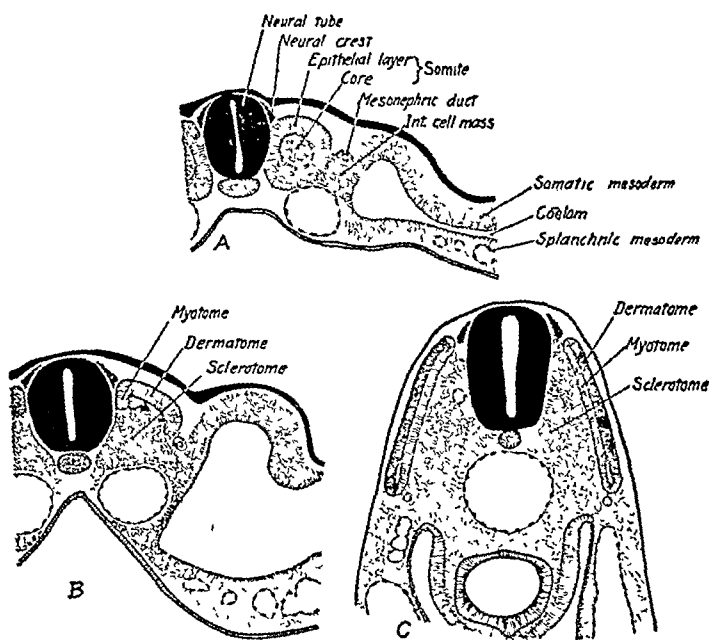


FIG. 53. Sections at three different levels through a chick embryo 48 hours old, drawn especially to show the early differentiation of the somite.

Mesothelium and Mesenchyme. Very early there differentiate two diverse histological forms of mesoderm, which it is convenient to keep in mind. Mesoderm in which the cells form a definite layer is called **mesothelium**, as, for example, the lining of the coelomic cavity and also the lining of the vascular system (though the latter is actually called endothelium). The second type, **mesenchyme**, develops very extensively in the embryo. It is a tissue of very loose structure com-

CHAPTER VIII

THE SUPPORTING TISSUES AND THE SKELETON

A THE ORIGIN OF THE SUPPORTING TISSUES

It is assumed that the reader knows the histological structure of the supporting tissues *reticular tissue, mucous tissue, loose connective tissue*, various forms of *dense connective tissue, cartilage, bone, and adipose*. All these supporting tissues (except adipose) have the common characteristic of widely separated cells between which is intercellular material. The intercellular material determines the properties of the tissues, though the cells of each also have definite distinguishing characteristics.

Histogenesis of Connective Tissue

All the supporting tissues come from mesenchyme, with the single exception of the neuroglia tissue of the central nervous system. This tissue is derived from the ectoderm and will be treated along with the nervous system.

The cells of mesenchyme are stellate, each cell having several long, slender cytoplasmic processes, which unite with the processes of other cells (Fig 54). The cells thus form a delicate network, the spaces of which are filled with a homogeneous, semifluid matrix. The various adult supporting tissues are derived from this mesenchyme by the development of different kinds of intercellular substance, which give the properties of flexibility or rigidity, elasticity or lack of it, which characterize the different tissues of this group. It is not the purpose here to describe in detail just how each kind of intercellular matter is produced, and, in fact, there is considerable difference of opinion concerning some points. It is agreed by all that the mesenchyme cells play an important part in the process, but it is not agreed whether the intercellular fibers and matrix arise as inter- or intracellular products.

B THE DEVELOPMENT OF BONE (OSSIFICATION)

On the basis of origin there are two kinds of bones, *membrane bones* and *cartilage bones*, but their final histological structure is identical. Moreover the essential nature of the ossification process (the forma-

two sheets of mesoderm which have been produced by the primitive streak (Fig. 50), but it also includes cells from probably two other sources. In embryos of the fourth week there is a migration of ectoderm cells from the neural crest of the head region; these cells become mesenchyme. The exact amount of their contribution is unknown, because the cells soon become indistinguishable from the other mesenchyme cells. In embryos of birds and the lower groups of vertebrates, there is also a contribution from the entoderm in the form of migrant cells from the fore gut, which also become mesenchyme, and it is quite probable that such may also be the case in the human embryo.

The preceding paragraphs give a somewhat sketchy picture of the diversified development in form and structure attained by the mesoderm even in early embryonic stages. The chapters to follow will add to the picture by describing the great range of adult anatomical and histological structures which develop from mesoderm. An outline of these structures is given in Table 9, page 276.

It will by this time be evident to the reader that the three germ layers are by no means sharply distinct from each other at all times, and that the mesoderm, especially, has a complicated origin. In extra-embryonic regions the relations are even less diagrammatic than in the embryo. Nevertheless the concept of germ layers has much of reality and to the student of embryology is very useful in bringing order into the study of development, as he traces the unfolding of the complicated adult organs from the primitive early tissues.

It is of interest to note that in the embryos of birds an earlier differentiation of mesodermal material than that described for human development is recognizable. It has been demonstrated by experimental methods that in the early avian blastoderm, before the establishment of the mesoderm as a separate layer, there are in the ectoderm certain "presumptive" mesodermal areas, representing the notochord and the axial, intermediate, and lateral mesoderm. These areas lie to either side of the primitive streak, and the mesodermal layer is produced by migration of this presumptive mesodermal tissue through the primitive streak from the ectodermal level to the mesodermal level. Though the mesoderm emerges from the primitive streak, it is not produced by proliferation of undifferentiated cells in the streak, as it would seem from cursory examination of sections through embryos; the mesoderm has an earlier origin which is not so readily observed. A quite comparable early origin of mesodermal material has also been observed in amphibian embryos.

fibers calcify and the osteoblasts deposit bone matrix upon the calcified fibers, thus producing the primary cancellous bone. This is known as intramembranous ossification. The dense outer tables of such bones are formed by osteoblasts in the periosteum surrounding the early cancellous bone, a process called subperiosteal ossification. The osteoblasts and other cells of the marrow develop from connective tissue cells derived from mesenchyme.

Development of Cartilage Bones Most bones are cartilage bones, typified in the long bones of the limbs. In their development the early mesenchyme masses develop into hyaline cartilages representing the bones in form and position. Cartilage is rigid enough to support the young embryo and has the capacity for growth which bone tissue lacks. These cartilages are gradually enveloped and replaced by bone tissue, the cartilage meanwhile continuing to grow until full adult size of the bones is attained. In the ossification of cartilage bones both subperiosteal and endochondral ossification are operative.

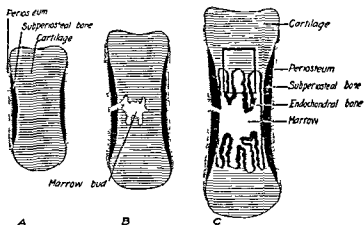


FIG 56 Three diagrams showing the early stages of ossification as seen in a longitudinal section of a cartilage bone. Bone shown in black, cartilage by parallel lines. A, a cylinder of subperiosteal bone has formed about the middle of the cartilage. B, a bud of primary marrow is shown invading the cartilage. C, ossification is progressing toward both ends of the cartilage. The rectangle marks the position of the area shown in Fig. 58.

1 Subperiosteal Ossification In most cartilage bones the earliest bone tissue is deposited by osteoblasts in the perichondrium, resulting in the formation of a cylinder of bone about the mid region of the cartilage (Fig. 56). The perichondrium, now the periosteum, continues to produce bone tissue as a thickening and elongating cylinder. Thus subperiosteal ossification generates the dense bone of the shafts of long bones and is responsible for the increase in thickness of bones.

tion of bone tissue) is the same in the two kinds. In both, the bone matrix is produced by cells known as osteoblasts (bone-forming cells) which in turn are developed from mesenchyme cells. Some of the osteoblasts become enclosed in the bone matrix while it is forming and are thenceforth known as osteocytes (bone cells). Bone tissue once formed has no power of growth; bone cells do not divide. Bone tissue increases in amount only by the deposition of more bone tissue

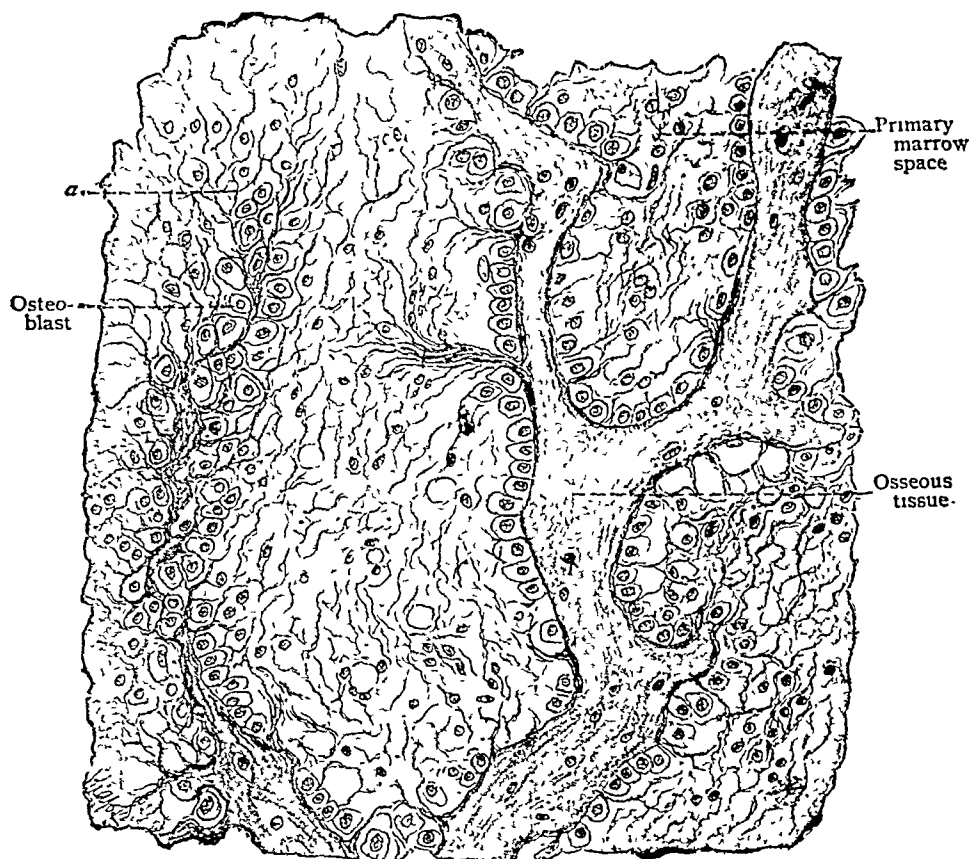


FIG. 55. The development of membrane bone (From Böhm, Davidoff, and Huber's *Histology*, W. B. Saunders Co., Philadelphia.)

upon its surface. Bones maintain proper shape by the deposition of bone tissue at some places and its removal from others. Membrane bones are preformed as masses of connective tissue. Cartilage bones are preformed as hyaline cartilages. In all bones ossification begins at certain centers of ossification, usually more than one for each bone, whence bone formation spreads until the entire bone is formed.

The Development of Membrane Bones. Membrane bones occur only in the skull. They are usually irregular in shape. Such bones are preformed as masses of fibrous connective tissue. The bundles of

steps of the process are complicated but orderly, and the various phases occupy definite zones as follows (1) Zone of undifferentiated cartilage cells, from which the cells of the following zone are con-

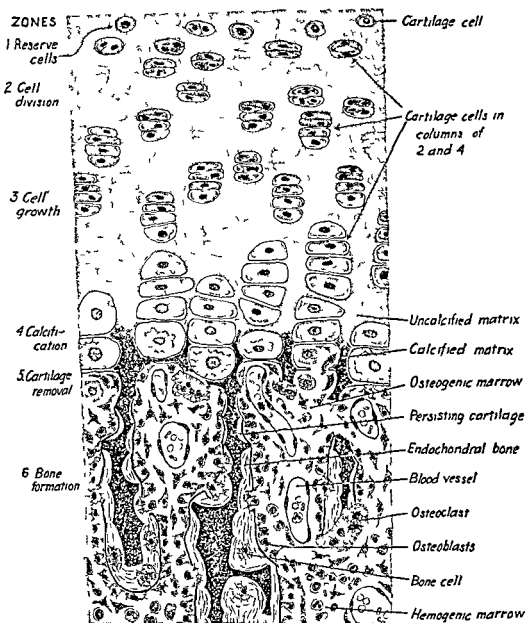


FIG 58 Details of endochondral ossification as seen in young cat. Longitudinal section highly magnified (like area in rectangle in Fig 56). Comparable to epiphyseal cartilage in any growing bone.

stantly replenished (2) Zone of cell multiplication, where repeated mitotic divisions produce columns of flattened cells (3) Zone of cell growth, where the flattened cells increase to several times their

Subperiosteal ossification is of the intramembranous type; the cartilage is not involved in it.

2. *Endochondral Ossification.* Endochondral ossification is responsible for the elongation of bones. It produces the cancellous bone tissue of the enlarged articular extremities. It usually begins a little later than subperiosteal ossification when marrow buds from the periosteum bore into the cartilage model about midway between the ends (Fig. 56*B*). The marrow then burrows toward the ends of the cartilage, destroying much of the cartilage tissue and depositing bone tissue upon the calcified remnants (Figs. 56 and 58). In childhood secondary centers of ossification develop in the cartilaginous extrem-

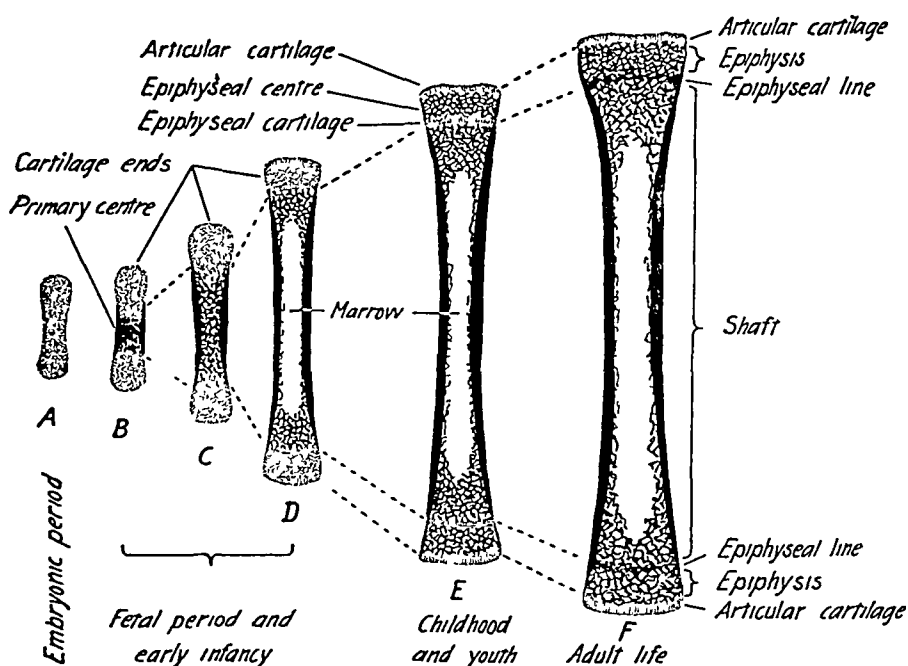


FIG. 57. Simple diagrams showing the entire development and growth of one of the long bones of the extremities from the cartilage stage to maturity. Bone is shown in black; cartilage in stippled shading.

ities (Fig. 57*E*), dividing each cartilage mass into two parts: (1) the articular cartilage, covering the articular surface, and (2) the epiphysal or growth cartilage, which is responsible for the elongation of the bone. When full length is attained, the denser epiphysal line marks the former position of the epiphysal cartilage (Fig. 57*F*). The marrow cavity is formed and expanded by appropriate removal of bone internally as it is added externally.

The histological details of the growth of the epiphysal cartilage and its replacement by bone are illustrated in Fig. 58. The various

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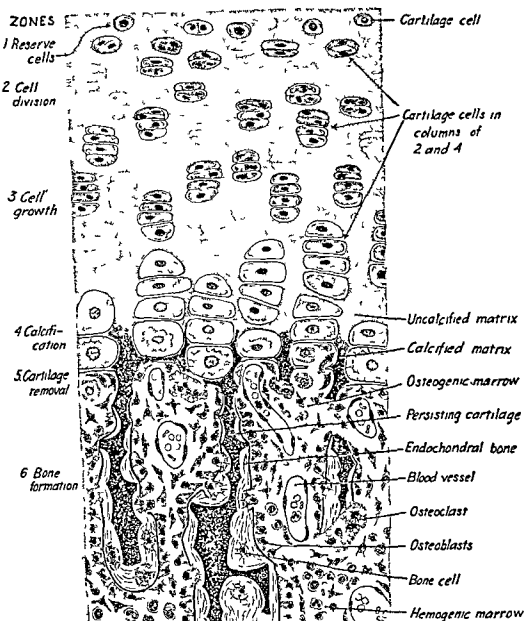


FIG 58 Details of endochondral ossification as seen in young cat Longitudinal section highly magnified (like area in rectangle in Fig 56) Comparable to epiphyseal cartilage in any growing bone

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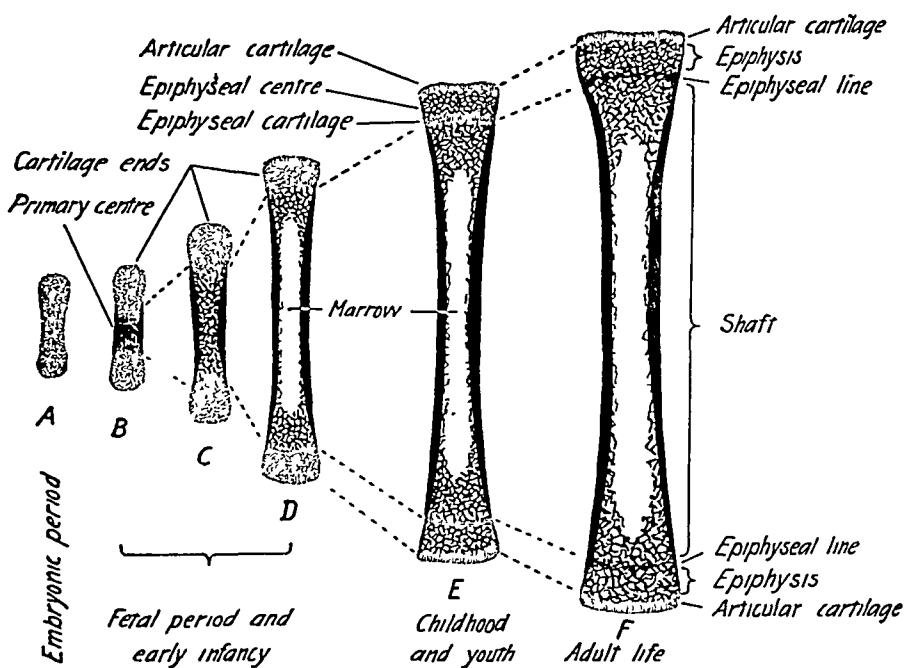


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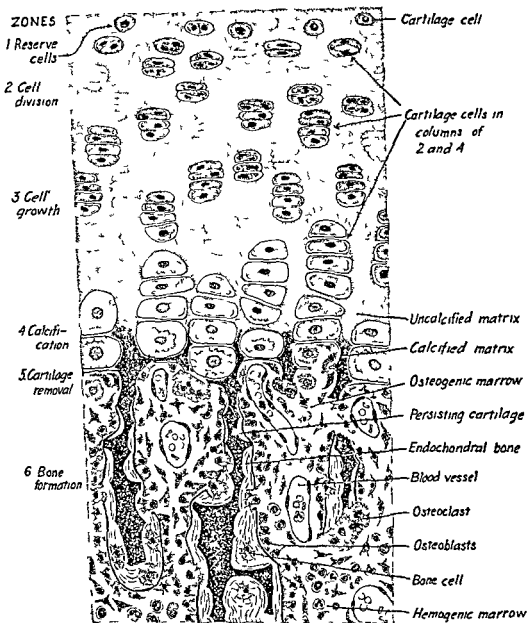


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former thickness. (4) **Zone of calcification.** When the cells have attained their full thickness, the matrix between the cell columns becomes calcified. (5) **Zone of cartilage removal.** Calcification is followed closely by destruction of the cartilage cells and part of the matrix. Osteoclasts seem necessary for the removal of calcified matrix but not for other parts of cartilage. (6) **Zone of bone deposition.** Upon the persisting calcified cartilage trabeculae, bone tissue is deposited, thus forming the beginning of the primary spongy bone. The above processes follow each other in orderly sequence, the cartilage causing the elongation of the bone and the marrow making use of the growing cartilage as a foundation for the new bone tissue.

Special attention should be directed to the marrow with its many types of cells in close proximity to each other, all of which are developed by specialization of mesenchyme cells. The cells concerned with the removal of cartilage and the building and removal of bone, notably osteoblasts and osteoclasts, in addition to numerous smaller cells with less evident characteristics, appear early and have already been mentioned (Fig. 58). A little later there are produced the many types of cells involved in the development of blood cells (erythrocytes, leucocytes, and platelets) described more fully in Chapter XVI. Among these cells are also the supporting elements of the marrow and the adipose cells which soon develop, as well as the tissues of the vascular channels. Figure 58 pictures in an incomplete manner these types of cells in relation to the cartilage and bone.

Development of the Joints. Joints arise from the mesenchyme between adjacent developing bones, the two kinds developing as follows: (1) **Synarthroses** (joints allowing little or no movement). In such joints the mesenchyme between the developing bones develops into a small amount of connective tissue, as in the sutures of the skull, or into cartilages, like the fibrous cartilages between the vertebrae. (2) **Diarthroses** (joints with a synovial cavity allowing free movement). In the development of such joints, the central portion of the mesenchyme between the developing bones degenerates, forming a cavity, while its outer portion develops into dense connective tissue, thus forming the capsule connecting the periosteum of the adjacent bones and enclosing the joint cavity. The cells on the inner surface of the capsule become flattened to form the **synovial membrane**. The origin of the articular cartilage has already been described.

C. THE DEVELOPMENT OF THE SKELETON

The development of the various parts of the skeleton will now be described, not in great detail, but in a general way intended to present

a definite picture of the main features of the prenatal history of the skeletal system

The Appendicular Skeleton

The skeleton of the arms and legs develops in the limb buds. First the mesenchyme along the central axis of the developing limb becomes more dense than the rest. Then there develop from it separate cartilages, representing the future bones of the limbs. In these cartilages ossification takes place. Each bone in the limbs has one primary center of ossification except the innominate, which has three. Nearly

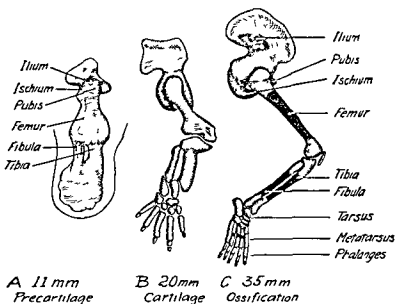


FIG 59 Three stages in the development of the innominate bone and the bones of the leg in the human embryo. A, embryo 11 mm long (6 weeks), shows the general precartilage mass in which the separate cartilages are beginning to develop. B, embryo 20 mm long (7 weeks) shows the cartilages at about their greatest development but no bone has yet formed. C, fetus 35 mm long (9 weeks), certain of the primary centers of ossification have appeared (Redrawn from Bardeen in *Am Jour Anat*)

all have also one or more secondary centers which give rise to the articular ends of the bones and to various irregularities of form.

The Leg The precartilage mass for the bones of the leg is well developed at six weeks, and some of the cartilages are already forming in it (Fig 59A). At seven weeks the cartilages for nearly all the bones have formed, and the separate elements of the adult skeleton are clearly seen, though as yet no bone has been formed (Fig 59B). Ossification begins in the seventh week (Table 3, p 103), the condition at the end of the week being shown in Fig 68.

The innominate bone has three primary ossification centers, all of which appear before the fifth month. These produce separate bones, the ilium, the ischium, and the pubis, which unite into a single bone.

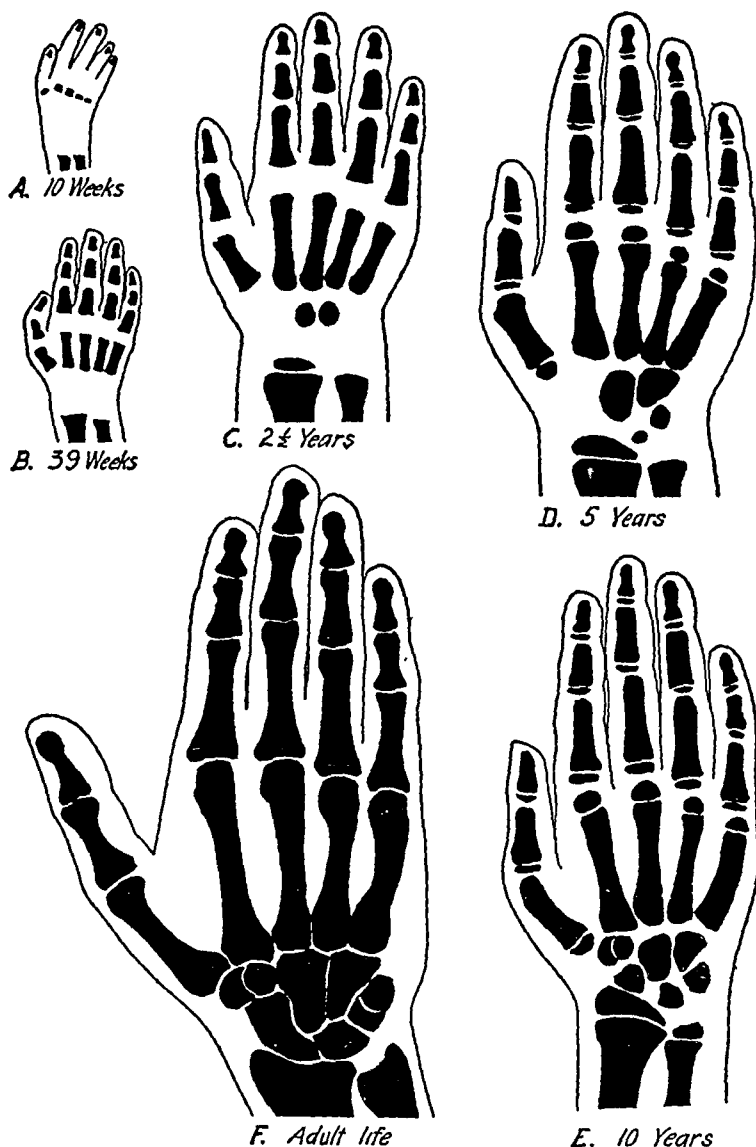


FIG. 60. A series of drawings to show the progress of ossification in the hand. (A, from a cleared preparation B, C, D, E, from Kollmann's *Handatlas*. F, from X-ray plate.)

About seven secondary centers, which do not appear until puberty, also contribute to the formation of the bone. Primary centers for all the bones of the leg and foot, except for the patella and five of the seven bones in the ankle, appear before birth (Tables 3 and 4, pp. 103

and 105) The secondary centers appear after birth, except for the distal end of the femur, which forms shortly before birth. The progress of ossification of the leg bones up to the fifth month is shown in Figs 68, 69, 70, and 72, though the details on the foot are not shown in all these figures.

The Arms The skeleton of the arm follows essentially the same course of development as does that of the leg. The clavicle is the first bone in the body to begin ossification, its primary center appearing in the seventh week. Its one secondary center does not appear until the twentieth year. The scapula has one primary center, which appears late in the ninth week, and seven secondary centers, which appear from the first year to puberty. The primary centers for the arm and hand appear by the end of the third month, except for the eight bones of the wrist, which begin to ossify from the first to the tenth years (Tables 3 and 4). Figures 68, 69, 70, and 72 show the ossification of the arm up to the fifth month. Figure 60 shows in greater detail the ossification of the hand.

The Vertebrae and Ribs

The notochord begins its development late in the third week. It forms the earliest vertebral column of the embryo. The vertebral column of the adult, however, is not a derivative of the notochord, but a new structure which forms around it and replaces it, the only remnants of the notochord persisting in the adult being the pulpy nuclei in the intervertebral discs.

The vertebrae and ribs develop from the mesenchyme of the sclerotomes in the following manner. The sclerotomes, as first formed from the somites, are denser masses of mesenchyme on the right and left sides of the notochord (Fig 53, p 82). The sclerotomes lie opposite the myotomes and alternate to the intersegmental arteries, as seen in Fig 61A, which shows these structures as viewed from above. Although the sclerotomes give rise to the vertebrae, a pair of sclerotomes does not develop into a vertebral segment. Instead new bodies are formed by the fusion of the caudal half of each sclerotome with the cranial half of the sclerotome below it. The new bodies formed by these fusions are the paired primordia of the vertebrae (Fig 61). These paired, right and left masses of mesenchyme fuse around the notochord to form the bodies of the vertebrae (Fig 62). As the primordia of the vertebrae are thus forming, the middle zone of each sclerotome becomes looser and gives rise to the fibro-cartilaginous intervertebral discs (Fig 61). The vertebrae thus formed are alternate to the myotomes, instead of opposite them, as were the sclerotomes (Fig 61).

The arches of the vertebrae arise as two dorsal outgrowths from each body, which grow up around the neural tube. A pair of processes also grows out from each body in a latero-ventral direction. These are the costal processes, which will develop into the ribs (Fig. 62).

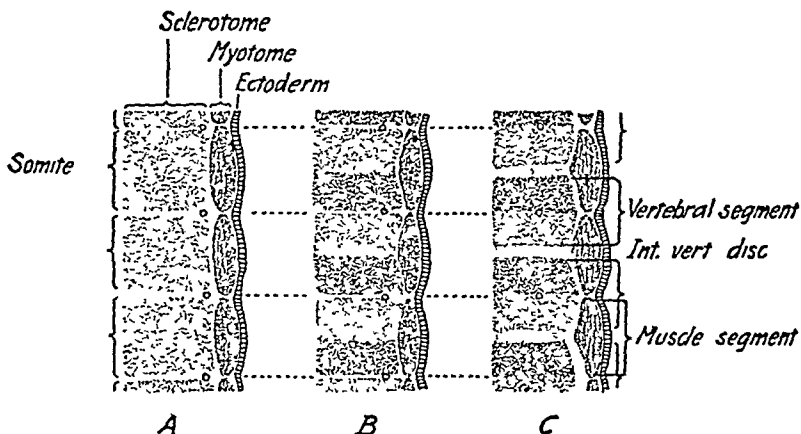


FIG. 61. Diagrams showing the formation of the rudiments of the vertebrae from portions of two adjacent sclerotomes, as seen from dorsal view.

Cartilage now forms from the mesenchyme, beginning in six centers, two in the body, two in the arch, and one in each costal process (Fig. 62). The cartilage spreads from these centers until each vertebra becomes a solid mass of cartilage.

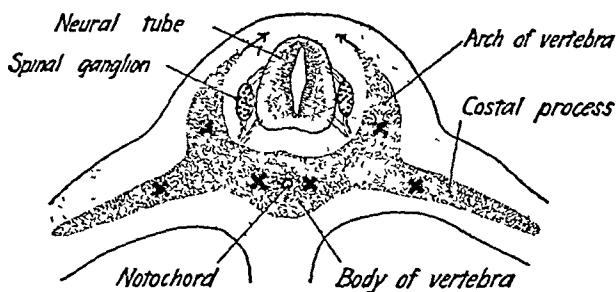


FIG. 62. Cross-section through the mesenchyme stage of a vertebra, as seen in pig embryo 12 mm long. The six centers of cartilage formation will appear at the places marked X. The ossification centers will appear later at about the same places, except that there is only one ossification center in the body of the vertebra.

Ossification in each cartilaginous vertebra begins in five primary centers, one in each costal process, from which develop the ribs, one in the body, and one in each half of the arch.

The ribs begin to ossify about the middle of the ninth week, the sixth and seventh ribs being the first to appear. The others follow within the next five days (Table 3, p. 103). Ossification in the arches

begins about four days later than in the ribs. The process begins first in the cervical region, whence it spreads rapidly caudad. Ossification in the bodies begins one day later than in the arches. The lower thoracic and upper lumbar segments are the first to begin to ossify, whence the process spreads in both directions. The centers for both arches and bodies are formed in rapid succession, except those in the coccygeal region, which do not appear until about the time of birth.

Figure 69 shows almost the beginning of ossification of the vertebrae, when only ten centers have appeared in the arches. Ossification has already begun in all the ribs. Figure 70 shows a fetus in which the arches have formed in segments 1-25 and the bodies in 6-26. Figure 71 shows these centers in a ventral view of the same fetus. Figure 72 shows a fetus in which most of the centers have appeared for both bodies and arches.

At the time of birth the three centers in each vertebra are still distinct, being yet separated by cartilage. During the first year the centers in the right and left halves of the arch unite dorsally, thus completing the arch, but it is not until the third to the sixth years that the arch unites with the body. At puberty there appear two epiphyseal centers in the body of each vertebra as well as certain others in the arches. Ossification of the vertebrae is completed at about the age of twenty-five years.

The foregoing account applies in its fullness only in the thoracic region, where vertebrae and ribs develop in what may be called the typical fashion. The modifications in other regions are of interest.

The second vertebra, the axis or epistropheus, is modified in that the body of the first vertebra unites with it to form the dens or odontoid process. The first vertebra, the atlas, accordingly lacks a body, its ventral arch ossifying from a center which appears during the first year after birth. In all the cervical vertebrae, the costal processes, instead of forming ribs as they do in the thorax, fuse with the vertebrae at both ends, thus forming the foramina through which the vertebral vessels pass. In the lumbar region the costal processes unite with the vertebrae to form the small accessory processes. The five sacral vertebrae and their costal processes fuse to form a single bone, the sacrum. The costal processes form the pars lateralis, the part through which the sacrum articulates with the innominate bones.

The postsacral vertebrae, four or five in number, are poorly developed and variable. They usually fuse into a single bone, the coccyx, but ossification does not begin until the first to the tenth year. The coccyx is the adult remnant of the tail of the embryo and corresponds to the protruding tail of other vertebrate animals.

The Sternum

The sternum arises from two longitudinal bands of mesenchyme which become cartilaginous, forming the two sternal bars. Right and left bars soon fuse into a single bar, the **sternum**. Ossification takes place commonly from nine centers which appear in succession from the third to the ninth month of fetal life, except for the center in the xiphoid process, which does not appear until the third year. Figure 72 shows three of these early centers. The ossification of the sternum is not complete until middle life or old age. Eight or nine pairs of ribs join the sternal bars very early in their development, but only seven pairs retain connection with the sternum.

The Skull

The Subdivisions of the Skull. The skull develops from mesenchyme in the head region. Its development is complicated, as that of so elaborate a structure would necessarily be. Nearly every bone of the skull develops from several separate centers of ossification. Moreover, the adult human skull includes two parts with separate origins and different functions, these two so intimately united in the adult as to give little indication of separate origins: (1) the **cranium** or brain case, surrounding the brain and protecting the organs of hearing, sight, and smell, and (2) the **jaws**, belonging to the alimentary system. There is further complexity of development because both cranium and jaws include both cartilage bones and membrane bones. Although the first three or four somites lie in the head region, they degenerate early and seemingly play no part in the formation of the skull.

The Cartilage Bones of the Skull. In the embryo there is formed a cartilaginous skull of two distinct parts which very nearly correspond to the two parts of the adult skull: (1) the **chondrocranium** (the cartilage skull of the brain and sense organs), and (2) the **branchial cartilages** (the skeleton of the pharynx). These two parts may be better understood by reference to a familiar laboratory animal, the dogfish, the skull of which is wholly of cartilage, the cartilages of the branchial arches being united to the chondrocranium only by membrane (Fig. 63).

The human chondrocranium is a cartilaginous structure which begins to form early in the second month. It never completely encloses the brain as it does in the dogfish but has the form of an irregular, basket-like structure which lies ventral to the brain, and hardly extends up on the sides at all (Figs. 64 and 66). Included in

the chondrocranium are the cartilaginous capsules which surround the developing inner ear (the otic capsule) and certain cartilages developed in connection with the olfactory organs. The anterior end of the notochord is embedded in the chondrocranium, but it extends only as far cephalad as the point marked by the sella turcica of the adult sphenoid bone.

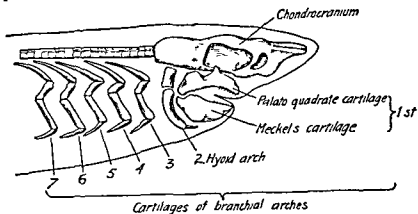


FIG 63 The skull of a dogfish, side view

Ossification of the chondrocranium begins late in the second month and results in the formation of the entire ethmoid bone and the inferior nasal concha, and portions of the sphenoid, temporal, and occipital bones (Figs 65 and 67).

The branchial cartilages develop in the mesenchyme of the wall of the embryonic pharynx between the branchial grooves. They correspond to the seven cartilaginous arches of the dogfish, in which animal they form the jaws and support the gills (Fig 63). In the human embryo the branchial cartilages appear in five of the arches during the latter part of the second month, but they never attain any considerable size. They are shown at about their greatest development in Fig 64.

In the first arch of the dogfish there are two stout cartilages, the skeleton of the jaws. In the human embryo the maxillary process of the first arch (upper jaw) produces only the small quadrate cartilage, which ossifies to form the incus of the middle ear (Figs 64 and 65). In the mandibular process (lower jaw) a slender rod, Meckel's cartilage, develops, extending outward from the auditory capsule. All this cartilage degenerates except the proximal end, which persists to become the malleus of the middle ear (Figs 64, 65, and 181, p 120).

In the second arch a slender cartilage forms, which, like Meckel's cartilage, extends outward from the auditory capsule (Fig 64). Its proximal end forms the stapes, the remainder develops into the

The Sternum

The sternum arises from two longitudinal bands of mesenchyme which become cartilaginous, forming the two sternal bars. Right and left bars soon fuse into a single bar, the sternum. Ossification takes place commonly from nine centers which appear in succession from the third to the ninth month of fetal life, except for the center in the xiphoid process, which does not appear until the third year. Figure 72 shows three of these early centers. The ossification of the sternum is not complete until middle life or old age. Eight or nine pairs of ribs join the sternal bars very early in their development, but only seven pairs retain connection with the sternum.

The Skull

The Subdivisions of the Skull. The skull develops from mesenchyme in the head region. Its development is complicated, as that of so elaborate a structure would necessarily be. Nearly every bone of the skull develops from several separate centers of ossification. Moreover, the adult human skull includes two parts with separate origins and different functions, these two so intimately united in the adult as to give little indication of separate origins: (1) the **cranium** or brain case, surrounding the brain and protecting the organs of hearing, sight, and smell, and (2) the **jaws**, belonging to the alimentary system. There is further complexity of development because both cranium and jaws include both cartilage bones and membrane bones. Although the first three or four somites lie in the head region, they degenerate early and seemingly play no part in the formation of the skull. ✓

The Cartilage Bones of the Skull. In the embryo there is formed a cartilaginous skull of two distinct parts which very nearly correspond to the two parts of the adult skull: (1) the **chondrocranium** (the cartilage skull of the brain and sense organs), and (2) the **branchial cartilages** (the skeleton of the pharynx). These two parts may be better understood by reference to a familiar laboratory animal, the dogfish, the skull of which is wholly of cartilage, the cartilages of the branchial arches being united to the chondrocranium only by membrane (Fig. 63).

The human chondrocranium is a cartilaginous structure which begins to form early in the second month. It never completely encloses the brain as it does in the dogfish but has the form of an irregular, basket-like structure which lies ventral to the brain, and hardly extends up on the sides at all (Figs. 64 and 66). Included in

styloid process of the temporal bone, the stylohyoid ligament, and the lesser horn and body of the hyoid bone (Figs 64 and 65) The

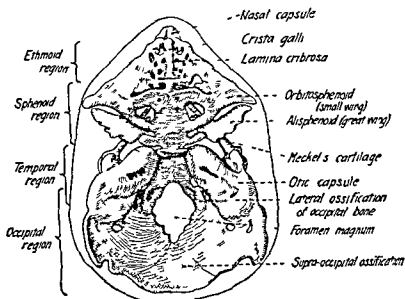


FIG 66 The human cartilaginous skull as seen from within the skull of a fetus 80 mm long (about 3 months) (After Gaupp in Hertwigs *Handbuch der Entwicklungsgeschichte der Wirbeltiere*)

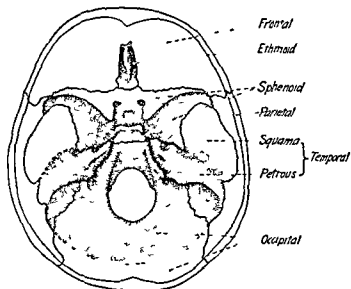


FIG 67 Base of adult skull from within The bones which develop from the cartilaginous skull are shaded those from membrane, unshaded (Redrawn from Lewis in *Cont to Emb*, Carnegie Inst, Washington)

cartilages of the third, fourth, and fifth arches are short and have no connection with the chondrocranium The third gives rise to the

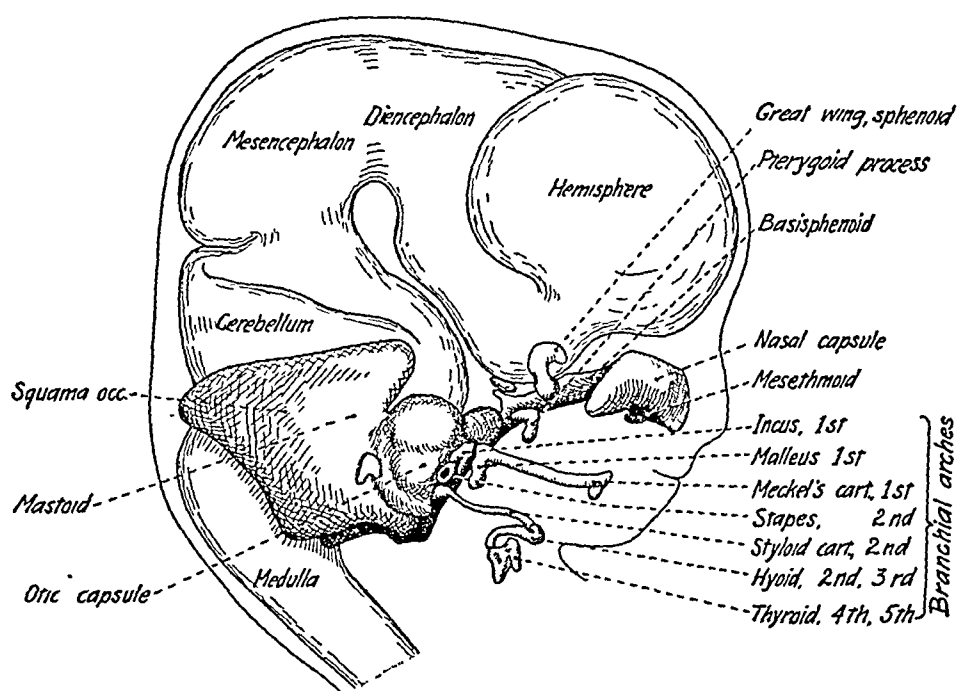


FIG. 64 The cartilaginous skull of a human embryo, 21 mm. long (about 7 weeks). The membranous covering of the brain has been removed. (Redrawn from Lewis in *Cont. to Emb.*, Carnegie Inst., Washington.)

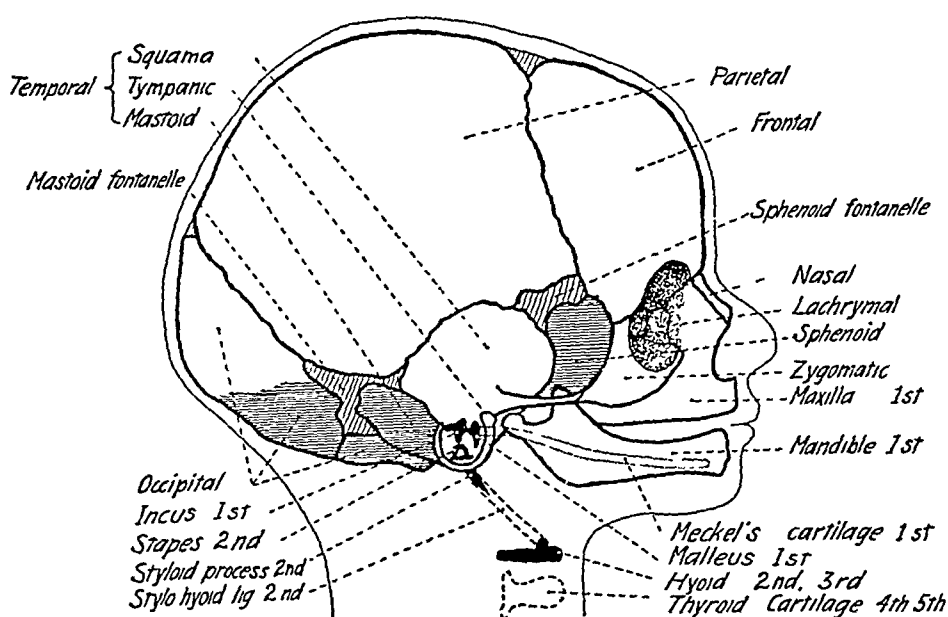


FIG. 65. Diagram of the late fetal skull. Cartilage bones from the arches are shaded black; cartilage bones from the chondrocranium, in horizontal lines; membrane bones, unshaded.

bones also develop from membrane. At the same time ossification is going on in the region of the face, where develop the vomer, nasal, zygomatic, and lachrymal bones (Fig 65)

The bones of the jaws also develop in membrane, for the cartilages in the first arch develop only slightly and do not give rise to bones, except the two auditory ossicles already mentioned. Accordingly, the maxilla and palatine bones develop from membrane in the maxillary process, and the mandible in the mandibular process.

The Fontanelles The frontal and parietal bones are at first small and do not touch each other or the other bones of the skull (Fig 69). As they increase in area, the intervening spaces are gradually obliterated until the bones come together along the sutures (Figs 70 and 72). In the angles between the parietals and the neighboring bones, however, there remain for some time certain unossified areas, the fontanelles, of which there are three main ones (Figs 65 and 72). These areas are covered only by membrane and are still present at birth, the last of them not closing until the third year. The bones forming the roof and sides of the skull do not become firmly united along the sutures until the close of the fourth year. Table 2 summarizes the development of the skull.

The General Progress of Ossification

The progress of ossification takes place with great regularity and uniformity in all individuals, so that the condition of the skeleton may be used as a definite measure of age. The primary centers of ossification, most of which form before birth, always develop in the same order, as do also the numerous secondary centers, most of which appear during infancy, childhood, and youth. Moreover the fusion of each secondary center with the primary centers takes place at a definite time, so that, from the beginning of ossification to the years of full maturity, the age of the individual may be judged with considerable accuracy by the skeleton.

The schedule of prenatal ossification is given in Tables 2 and 3, from which it may be seen at a glance in just what order the bones appear. The secondary centers are not included, but the facts concerning them are readily available in textbooks of anatomy.

The clavicle is the first bone to appear, its ossification beginning in embryos of 15 mm (seventh week). The external appearance of such an embryo is shown in Fig 26, p 47, from which it will be seen that ossification begins about the same time that the external appearance begins to change from the embryonic to the fetal form.

Ossification follows almost immediately, probably during the same

greater horn of the hyoid bone, and the fourth and fifth to the thyroid cartilage and possibly to some of the other cartilages of the larynx (Figs. 64 and 65).

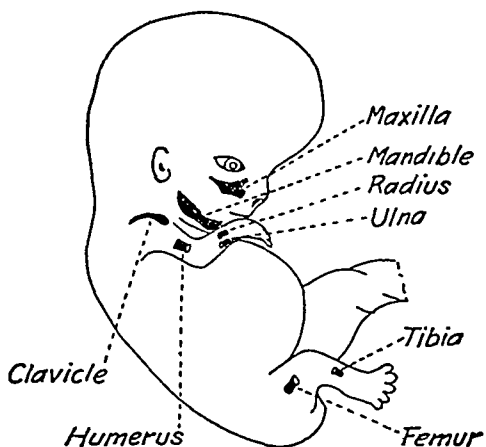


FIG 68. Outline drawing to show the extent of ossification in an embryo about 24 mm. long (about 8 weeks). X2. (Redrawn from Mall in *Am. Jour. Anat.*) This and the following four figures are designed to illustrate the general progress of ossification in the human fetus.

The Membrane Bones of the Skull. In addition to the parts of the adult skull which develop from these cartilages, important bones develop from membrane in both the cranial and pharyngeal regions. Bones from these different sources become so intimately united in the adult skull that they leave no evidence of different origins; in fact, bone from three sources enters into the makeup of a single bone, the temporal.

Membrane bones form by far the greater part of the skull, including the bones of the roof and sides of the skull and those of the face and jaws. The three largest bones formed from membrane are the

frontal and the two parietal bones. Their gradual growth is shown in Figs. 69, 70, and 72. Parts of the occipital, temporal, and sphenoid

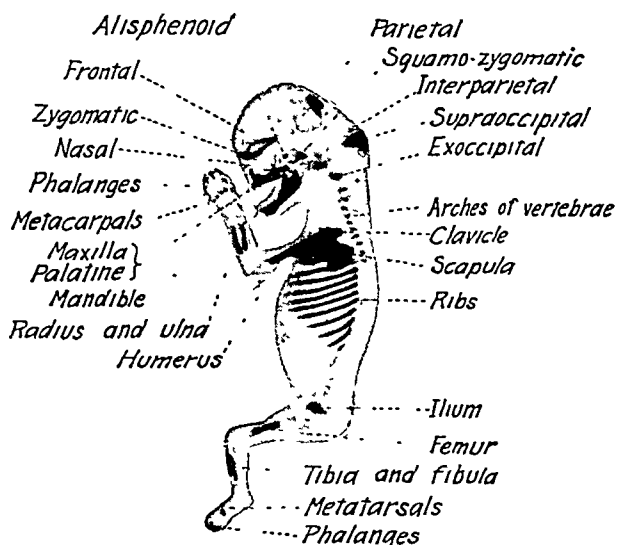


FIG. 69. Retouched photograph, natural size, showing most of the bones present in a fetus 38 mm. long (about 9½ weeks). Photograph made by transmitted light from a lateral half of a cleared fetus.

TABLE 3

TIMES OF APPEARANCE OF OSSIFICATION CENTERS IN THE HUMAN EMBRYO UP TO
A LENGTH OF 111 MM (15 WEEKS), AS DETERMINED BY MALL

CR Length mm. Age weeks	17 7	25 8	32 9	43 10	53 11	68 12	81 13	100 14	111 15
Frontal			x						
Parietal			x						
Supraoccipital			7x						
Exoccipital			x						
Interparietal			x						
Basoccipital				x					
Ethmoid									
Pterygoid			x						
Alisphenoid			x						
Orbitsphenoid						x			
Basphenoid						x			
Squamo-zygomatic			x						
Tympanic ring				x					
Petrous									
Lachrymal						x			
Nasal			x						
Inferior nasal concha									
Vomer			x						
Zygomatic			x						
Maxilla	x								
Premaxilla		x							
Palatine			x						
Mandible	x								
Hyoid									
Auditory ossicles									
Ribs			xxx	xx					
Arches of vertebrae				xxxxxx	xxxxxx	1st to 27th	Others later		x
Bodies of vertebrae				xxxxxx	xxxxxx	2nd to 29th	Others later	xxx	
Sternum									
Clavicle	x								
Scapula			x						
Humerus	x								
Radius	x								
Ulna		x							
Carpals									
Metacarpals				xx					
Phalanges 1st row				xxxxx					
2nd row						xxxxx	xx		
3rd row				xx					
Ilium			x						
Ischium									
Pubis									x
Femur	x								
Patella									
Tibia	x								
Fibula			x						
Tarsals									
Metatarsals				x					
Phalanges 1st row									
2nd row						xx			
3rd row				xxxxx	xxxxxx	xxxxxx	xxxxxx	x	

TABLE 2
ORIGIN OF THE BONES OF THE SKULL

<i>Adult Bones</i>	<i>In Cranial Region</i>		<i>In Branchial Region</i>	
	<i>Cartilage</i>	<i>Membrane</i>	<i>Cartilage</i>	<i>Membrane</i>
Ethmoid	Whole bone			
Inferior nasal concha	Whole bone			
Sphenoid	Body Great wing (part) Small wing Hamular process	Great wing (part) Pterygoid process		
Occipital	Basal part Lateral part Squamous part below superior nuchal line	Squamous part above superior nuchal line		
Temporal	Mastoid part Petrus part	Tympanic part Squamous part	Styloid process from 2nd arch	
Frontal		Whole bone		
Parietal		Whole bone		
Nasal		Whole bone		
Lachrymal		Whole bone		
Zygomatic		Whole bone		
Vomer		Whole bone		
Maxilla				In max process of 1st arch
Palatine				In max. process of 1st arch
Mandible				In mand process of 1st arch
Incus			1st arch, quadrate cart.	
Malleus			1st arch, Meckel's cart.	
Stapes			2nd arch	
Stylohyoid lig			2nd arch	
Hyoid			Lesser horn, 2nd Corpus, 2nd Greater horn, 3rd	
Thyroid cart.			4th and 5th arches	

During the remaining three-fourths of prenatal life, forty-three other bones make their appearance (Tables 3 and 4). At the time of birth twenty-nine bones remain still represented by cartilage, the ossification of which begins during the years of infancy and childhood. The wrist and ankle include nearly all the bones which have not begun ossification before birth.

Though nearly two-thirds of the bones, including most of the large bones of the head, trunk, and limbs, have begun ossification by the close of the tenth week, the general appearance of the fetus of this age hardly gives this impression, because the centers of ossification

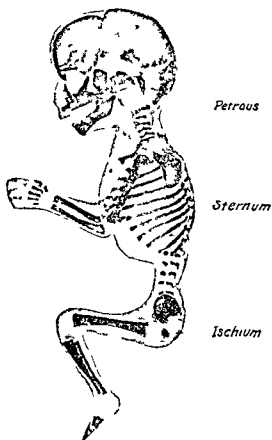


FIG 72 Retouched photograph showing most of the bones present in a fetus 140 mm long (about 17 weeks) $\times \frac{1}{2}$

are still small, so that much space is left between adjacent bones (Fig 69). From this time on, the skeleton becomes steadily more conspicuous, a condition due partly to the appearance of new bones, but in larger degree to the growth of the bones which formed during the early weeks of ossification (Figs 70 and 72).

day, in the maxilla and mandible (Table 3). Then follow the pre-maxilla (the incisive part of the maxilla), the humerus, and the femur on the fiftieth day, almost immediately thereafter the radius and tibia, and a few days later the ulna. This makes a total of fifteen separate bones which have begun to ossify by the end of the second month, that is, at the beginning of the fetal period, when the individual has a length of 25 mm. or 1 inch (Fig. 68).

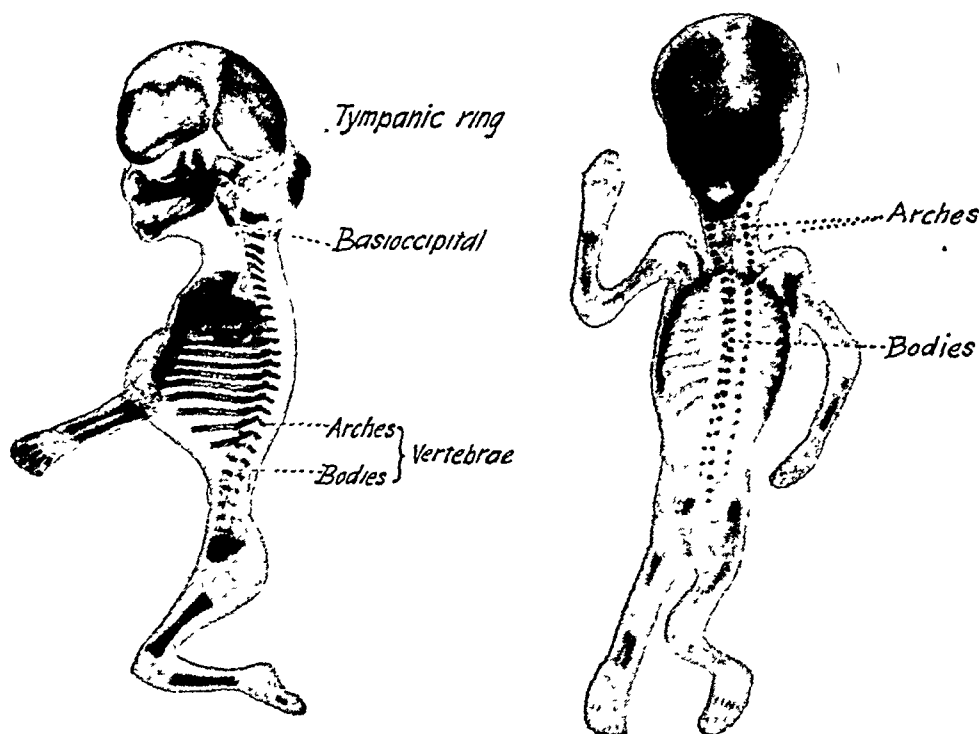


FIG. 70. Retouched photograph, natural size, showing most of the bones present in a fetus 60 mm. long (about $11\frac{1}{2}$ weeks).

FIG. 71. Retouched print from an X-ray photograph of the fetus shown in Fig. 70, natural size. Designed especially to show the ossification centers for the vertebrae. Centers for the arches have appeared in vertebrae 1-25; for the bodies in 6-27.

After this stage, the first two weeks of the fetal period are very fruitful in the production of new bones, for during this time no fewer than 116 separate bones have their beginnings. A list of these bones and of the order of their appearance is shown in Table 3. Thus it is seen that, during a little more than three weeks after the beginning of ossification, 133 bones, or just about two-thirds of the total number in the adult body, have appeared. Figures 68 and 69 show the progress of ossification during this period.

(rachischisis or cleft spine), a far more radical defect than spina bifida. Both ancrania and rachischisis are accompanied by grave defects in the brain and spinal cord (Fig 172, p 257). These anomalies develop when the neural groove fails to close in the affected regions. A rarer anomaly is characterized by complete division of vertebrae into right and left halves (anterior and posterior rachischisis), most common in cervical and upper thoracic regions. The condition produces a very short neck. Associated with this defect there is frequently, perhaps always, incompleteness of the diaphragm, allowing extensive displacement of abdominal viscera into the thorax. The embryological defect involved in the inception of this complex of anomalies is believed to be abnormal behavior of the neurenteric canal, that transient opening between the amniotic cavity and the yolk sac at the close of the third week (see Fig 15, p 38).



TABLE 4

TIMES OF APPEARANCE OF OSSIFICATION CENTERS WHICH
DEVELOP LATER THAN THE FIFTEENTH WEEK, INFORMATION
COLLECTED FROM VARIOUS SOURCES

Ethmoid	5th to 6th months
Petrous part of temporal	5th month
Inferior nasal concha	5th to 7th months
Hyoid	Late fetal life
Auditory ossicles	5th month
Sternum	4th month
Carpals	1st to 10th postnatal years
Pubis of innominate	5th month
Patella	3rd to 5th years
Tarsals: Calcaneus	6th month
Talus	8th month
Five other bones	Birth to 4th year
Second phalanx of toes	4th to 10th months

D. ANOMALIES

Many anomalies of the skeleton are produced either by failure of ossification centers to develop, by the formation of supernumerary centers, or by failure of centers to unite properly. Too great growth of the epiphyseal cartilages results in excessive elongation of the bones of the limbs and gigantism. Too little growth of the epiphyseal cartilages produces achondroplastic dwarfs with very short limbs. Extra fingers and toes sometimes develop.

The chondrocranium sometimes grows insufficiently, producing a deformed skull. In other cases fusion between bones of the skull may come too early, so that other types of deformity result. The palatine bones and palatine processes of the maxilla may fail to unite with the vomer on one or both sides, causing a cleft palate. Failure of the median nasal process to unite with the maxillary process on one or both sides produces a single or double hare lip, which sometimes involves the lip only, but may also involve the alveolar process of the maxilla between lateral incisor and canine teeth.

Variation in the number of vertebrae is not uncommon. There is sometimes an extra pair of ribs in the cervical region. Again, a pair may be wanting at either end of the series. *Spina bifida* is a condition in which certain vertebral arches are incomplete, allowing protrusion of the meninges to form a cyst containing cerebrospinal fluid. This condition is often recognized externally by a swelling at some point along the back.

The whole vault of the skull is sometimes wanting (*acrania*). Right and left halves of the vertebral arches often fail to unite

by the fusion of rows of granules which extend for a considerable distance through the syncytium. The fibrillae seem to multiply by longitudinal division and later the cross striations develop. Thus the syncytium gradually takes on the form of the cardiac muscle fibers with their anastomosing connections and intercalated discs.

Skeletal or Striated Muscle There are two beliefs as to the manner in which the multinucleated fibers of skeletal muscle arise. Some investigators maintain that the many nuclei of a fiber arise by mitotic division of the nucleus of one original myoblast, whereas others state that they arise by fusion of several myoblasts which unite to form a single muscle fiber. The fibrillae arise, as in cardiac muscle, by the fusion of rows of granules in the cytoplasm, increase in number by longitudinal division, and in due time take on the transverse striations.

B DEVELOPMENT OF THE VARIOUS GROUPS OF MUSCLES

The Skeletal Muscles

In this division are included all those striated muscles which are under the voluntary control of the central nervous system. The term skeletal is applied to these muscles because they produce motion in the parts of the body by reason of their attachment to the skeleton. Practically all the skeletal muscles can be recognized by the end of the seventh week. They soon attain the power of contraction, and as early as the fourth month the fetus has been known to make movements which were felt by the mother.

The Muscles of the Trunk In Chapter VII was described the breaking up of the mesodermal somite into the sclerotome, myotome, and dermatome (Fig 53, p 82). As pointed out in that chapter, the myotomes give rise to the muscles of the trunk but not to those of the head and limbs. The dermatomes, which in lower vertebrates give rise to the dermis of the skin, in the mammals unite with the myotomes and participate in the formation of the trunk musculature. In all there are formed about thirty-eight myotomes: three occipital, eight cervical, twelve thoracic, five lumbar, five sacral, and about five coccygeal or caudal.

The myotomes are arranged in a series along each side of the spinal column and give rise to muscle masses which at first have this same segmental arrangement. These muscle segments grow dorsad to come into relation with the vertebrae, and also extend ventrad around the body until right and left ones meet in the mid-ventral line. Such a condition is shown somewhat diagrammatically in Fig 73, and as it actually appears in a 9-mm human embryo in Fig 74.

CHAPTER IX

THE MUSCLES

Muscle tissue is widely spread in the body, forming parts of many organs. We are hardly justified, therefore, in speaking of a muscular system in the same sense as we speak of the digestive system or the nervous system. We might well recognize a *skeletal-muscle system*, because these muscles are organized, along with the skeleton, into a definite, coordinated system; but if we include all kinds of muscles, we go far beyond the bounds of one system. The development of muscles, accordingly, is a subject which can be understood fully only when studied in connection with the various systems of organs in which muscle tissue occurs. In this chapter, therefore, will be given a general account of the development of muscle tissue, together with reference to the various groups of muscles, but further description of most of these groups will be found in the chapters dealing with the organs in which they occur. Only the skeletal muscles will receive complete treatment.

Muscles are derived from mesoderm, except the few which are from ectoderm. More specifically, muscle comes from the embryonic tissue, mesenchyme (Fig. 54, p. 83).

A. HISTOGENESIS OF MUSCLE TISSUES

Smooth Muscle. Smooth muscle is the most primitive of the three forms of muscle. In its development some of the cells of the mesenchyme, known as *myoblasts*, become elongated and assume the spindle-shaped form of the cells of smooth muscle tissue. At the same time the cytoplasm undergoes changes which give it the power of strong contractility. Other mesenchyme cells between the myoblasts give rise to the interstitial connective tissue which binds the muscle fibers together.

Cardiac Muscle. Cardiac muscle develops from part of the splanchnic mesoderm which surrounds the endothelium of the early heart tube (Fig. 117, p. 165). In its development the cytoplasmic strands connecting the cells of the mesenchyme grow much thicker, so that the whole mass becomes a syncytial network in which cell boundaries are lost. At the same time the myofibrillae form in the cytoplasm

by the fusion of rows of granules which extend for a considerable distance through the syncytium. The fibrillae seem to multiply by longitudinal division and later the cross striations develop. Thus the syncytium gradually takes on the form of the cardiac muscle fibers with their anastomosing connections and intercalated discs.

Skeletal or Striated Muscle There are two beliefs as to the manner in which the multinucleated fibers of skeletal muscle arise. Some investigators maintain that the many nuclei of a fiber arise by mitotic division of the nucleus of one original myoblast, whereas others state that they arise by fusion of several myoblasts which unite to form a single muscle fiber. The fibrillae arise, as in cardiac muscle, by the fusion of rows of granules in the cytoplasm, increase in number by longitudinal division, and in due time take on the transverse striations.

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In lower vertebrates, such as fishes, this segmented condition persists with little modification in the adult. In man, however, such a condition is transient, for the regularity of the muscle segments is quickly lost; in fact, those at the anterior end of the body have progressed beyond this stage before those at the caudal end have reached it. In human embryos 9 mm. long (less than six weeks) the primitive segments are still clearly seen (Fig. 74), but less than two weeks later most of the adult muscles can already be recognized, as shown in an embryo 20 mm. long (Fig. 75).

Among the adult muscles derived from the myotomes, only the intercostals connected with the ribs and some of those associated with the vertebrae retain anything like the primitive segmentation. In the main the muscles of the trunk are of different sizes and lengths; they run in various directions; and they often occur in more than one layer. Moreover they are far more numerous than the myotomes, in that about 270 separate muscles develop from the thirty-eight pairs of myotomes.

The adult muscles develop from the primitive muscle segments by the operation of the following factors: (1) *Fusion*. Portions of two or more myotomes may fuse to form one muscle. (2) *Splitting* in either a vertical or a tangential direction. (3) *Degeneration* of part or all of certain myotomes to form fascias, ligaments, and aponeuroses. (4) *Change of direction*. Originally the fibers of the muscle segments are oriented in a direction parallel to the long axis of the body (Fig. 74). Very few of them retain this primitive direction. (5) *Migration*. Muscles frequently migrate far from their original segmental position. Examples are the latissimus dorsi and the musculature of the diaphragm, both of which originate from myotomes in the cervical region.

Peculiarities of the nerve supply of some muscles find an explanation in these changes. Each spinal nerve grows out from the spinal cord into the myotome directly opposite it. Figure 74 shows that the spinal ganglia correspond to the myotomes in number. Thus each myotome receives its nerve supply while still in its original position; and when it migrates, splits, or fuses it still retains the same nerve connection. Thus is explained the course of such nerves as the phrenic from the cervical part of the spinal cord to the diaphragm, and the long subscapular from the seventh and eighth cervical nerves to the latissimus dorsi muscle.

The Muscles of the Limbs. The muscles of the limbs, like the bones of the limbs, develop from the unsegmented mesenchyme of the limb buds (Figs. 73 and 74). Inasmuch as the limb buds arise as thicken-

ings of the body wall (somatopleure), this mesenchyme is a part of the somatic mesoderm. Some observers have described a migration of scattered cells from certain myotomes into the limb buds, and it is possible that such cells play a minor part in the development of the muscles of the limbs. The nerve supply to the muscles of the limbs consists of spinal nerves which grow out from the segments of the

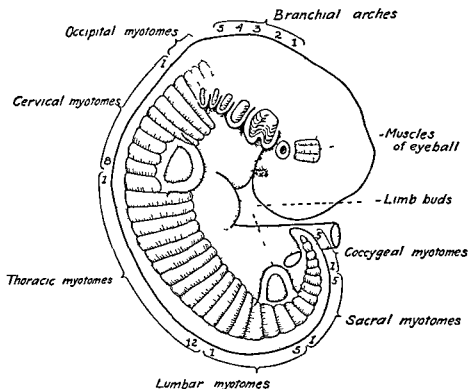


FIG 73 Diagram showing the origins of the different groups of skeletal muscles, based upon the outline of an embryo 7 mm long (the one shown in Fig 23). Shows all the myotomes, and the premuscle masses in the limb buds and branchial arches and for the extrinsic muscles of the eye

spinal cord opposite the limb buds. Figure 74 shows the nerves from seven segments extending into the leg bud. The rapidity with which the muscles of the limbs develop may be appreciated by comparing Figs 74 and 75, which cover a period of a little less than two weeks.

The Extrinsic Muscles of the Eyeball The six muscles of the eyeball and the levator palpebrae superioris, supplied by the oculomotor, trochlear, and abducens nerves, develop from a premuscle mass formed from mesenchyme close to the optic stalk (Fig 73). It is generally believed that these muscles represent three somites, innervated by three corresponding nerves, but no such somites have been observed in man or any other mammal. They are, however,

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Peculiarities of the nerve supply of some muscles find an explanation in these changes. Each spinal nerve grows out from the spinal cord into the myotome directly opposite it. Figure 74 shows that the spinal ganglia correspond to the myotomes in number. Thus each myotome receives its nerve supply while still in its original position; and when it migrates, splits, or fuses it still retains the same nerve connection. Thus is explained the course of such nerves as the phrenic from the cervical part of the spinal cord to the diaphragm, and the long subscapular from the seventh and eighth cervical nerves to the latissimus dorsi muscle.

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Four groups of muscles develop in the branchial arches, including about 110 muscles. They are supplied by five of the cranial nerves and develop as follows (1) *In the first arch* develop the muscles of mastication and a few other smaller muscles, all of which are supplied by the trigeminal (fifth) nerve, which is associated with this arch in

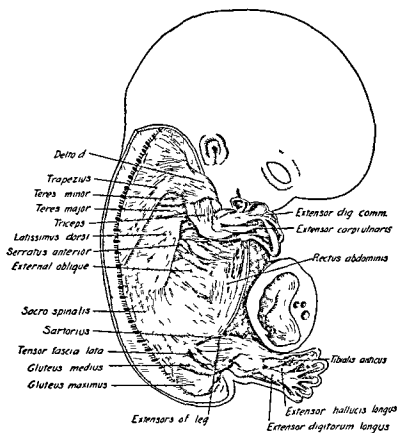


FIG 75 Lateral view of human embryo 20 mm long (over 7 weeks), dissected to show the superficial muscles (Redrawn from Bardeen and Lewis in *Am Jour Anat*) By this age the primitive segmentation of the myotomes has disappeared, and most of the adult muscles can be distinguished in both trunk and limbs

the embryo (Figs 73 and 169, p 247) It will be remembered that the bones of the jaws develop in this arch (2) *In the second arch* develop two groups of muscles, one group including a few small muscles which retain their relation to the hyoid bone, which develops in this arch, and the other and much larger group including the muscles of expression. During their development the muscles of expression undergo extensive migration into the region of the muscles from the first arch, which they overlie, they spread until they cover also almost the whole face and scalp (Fig 170, p 250) All the muscles developing in this arch are supplied by the facial (seventh) nerve (3) *In the third arch*

clearly seen in sharks. The observation upon sharks and the fact that the origins of the three nerves supplying these muscles in man correspond with those of other muscles which come from myotomes give support to the above view.

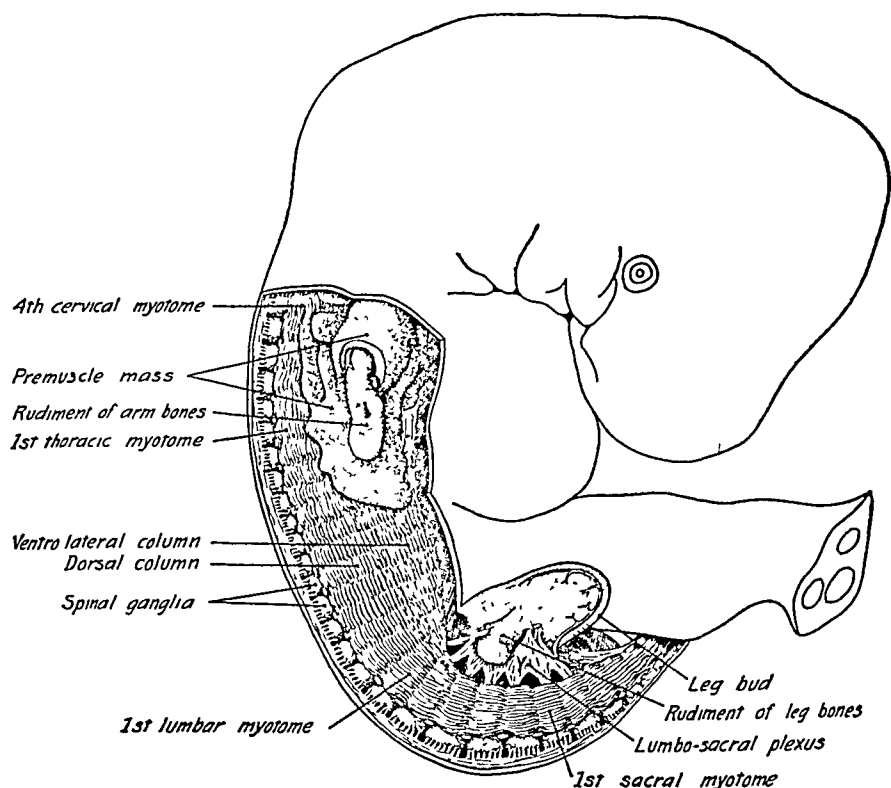


FIG. 74. Lateral view of a human embryo 9 mm. long (nearly 6 weeks), dissected to show the actual appearance of the myotomes and the premuscle masses in the limb buds. (Redrawn from Bardeen and Lewis in *Am. Jour. Anat.*)

The myotomes have already partly fused, but are still distinguishable. The premuscle masses of the arm and shoulder are clearly exposed, as is also the mesenchymal rudiment of the bones. The leg is less advanced than the arm. The spinal ganglia are seen to correspond to the myotomes. The lumbo-sacral plexus, including the five lumbar and the first two sacral nerves, is well shown.

The Muscles of the Head. The muscles of the head, both by their origin and by their nerve supply, show that they belong to a different group from other skeletal muscles. They are derived from mesenchyme of the branchial arches of the pharynx (part of the gut) and hence belong to the splanchnic rather than the somatic mesoderm. The pharynx and the upper portion of the esophagus are the only parts of the alimentary canal in which voluntary (striated) musculature is developed. The position of the premuscle masses with respect to the five branchial arches is shown in Fig. 73.

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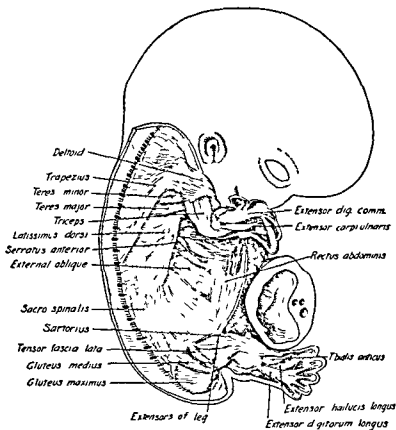


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develop certain muscles of the pharynx, which are supplied by the glossopharyngeal (ninth) nerve. The muscles which develop in this and the succeeding arches do not undergo much migration but remain associated with the pharynx and its adult derivatives. (4) *In the fourth and fifth arches* develop other muscles of the pharynx and those of the soft palate and larynx, which are supplied by the vagus (tenth) and accessory (eleventh) nerves.

The muscles of the tongue are supplied in the main by the hypoglossal (twelfth) nerve, which has led to the common view that these muscles are derived from myotomes in the occipital region (shown in Fig. 73), but recent careful investigations indicate that they more probably come from mesenchyme in the floor of the pharynx. The trapezius and sternocleidomastoid muscles, supplied by the spinal accessory nerve, are probably derived from the caudal end of the pharynx.

The Involuntary Muscles

In this division are classed the muscles which are under the control of the autonomic system, the group being thus based upon adult anatomical relations rather than upon common embryonic origin. All except the heart are composed of smooth muscle. Such muscle usually forms part of some other organ and will be studied more carefully when the various organs are discussed. The different groups of involuntary muscles are the following:

1. *The smooth muscle tissue of the digestive tract and urogenital organs* is derived from splanchnic mesoderm surrounding the entodermal gut tube and other epithelial rudiments of visceral organs.

2. *The smooth muscle tissue of the blood vessels* is derived from the mesenchyme surrounding the endothelial rudiments of the early vessels.

3. *The cardiac muscle of the heart wall* is derived from the mesenchyme of that part of the splanchnic mesoderm which surrounds the early heart tube. This is probably the earliest muscle in the body to become capable of strong, repeated contractions.

4. *The ciliary muscle of the eyeball* is developed from mesenchyme in the region of the optic cup.

5. *The erector muscles of the hairs* develop from mesenchyme of the dermis.

6. *The muscles of the iris* develop from part of the ectoderm of the optic cup. These muscles and those in the seventh group are the only ones which come from other than mesoderm.

7 *The muscles surrounding the epithelium of the sweat glands and of the mammary glands develop from ectoderm covering the surface of the body, the same source as the epithelium of the glands*

C ANOMALIES

There are many minor variations of muscles, most of which do not interfere with normal function. Others are more serious in their results. Anomalies of muscles include variations in form, position, and attachment and are probably the result of faulty migration, degeneration, or splitting of myotomes.

CHAPTER X

THE SKIN AND ASSOCIATED STRUCTURES

A. THE SKIN

The Epidermis. The stratified squamous epithelium of the epidermis is derived from the ectoderm covering the embryo. In its earliest form the ectoderm is a single layer of cuboidal cells, but by the end of the

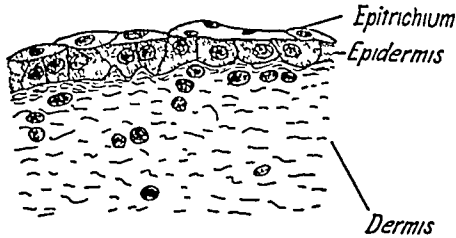


FIG. 76 Section through the skin of a fetus 50 mm long (about 11 weeks). (Redrawn from Pinkus in Keibel and Mall, *Human Embryology*, J B Lippincott Co, Philadelphia.)

first month it is composed of two layers, an outer, the periderm or epitrichium, made up of flat cells, and an inner or epidermal layer of somewhat larger cells (Fig. 76). The epitrichium persists until about the sixth month, when it is shed. The epidermal layer becomes highly stratified by about the fourth month and gradually the specialization into germinal, granular, clear, and horny layers takes place.

The Dermis or Corium. The fibrous tissue composing the dermis is derived from mesenchyme underlying the ectoderm (Fig. 76). It has commonly been stated that the dermis is derived from the dermatome of the somite, and such seems clearly to be its origin in some vertebrates, such as birds, but it is now generally believed that in mammals the dermatome gives rise to muscle and that the dermis comes from mesenchyme (somatic mesoderm) between the dermatome and the ectoderm. While the mesenchyme is developing into connective tissue, the layer becomes divided into the denser dermal layer and the looser subcutaneous layer.

B. THE NAILS

The nails arise as modifications of the developing epidermis. About the ninth week the rudiments of the nails appear as thickenings of the epidermis on the ends of the digits; these later migrate to the dorsal surface, where they become depressed areas bordered by the nail folds (Fig. 77). A layer of ectoderm corresponding to the stratum lucidum of the epidermis becomes converted into the nail body, which is at first

covered with the cells of the horny layer, known as the eponychium (Fig 77) The nails correspond to the hoofs and claws of lower mammals, and it is of interest in this connection that for a time in the fetus

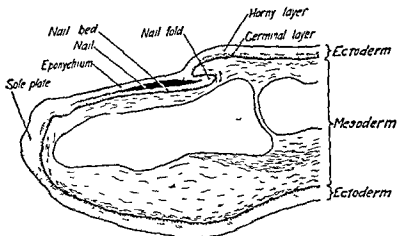


FIG 77 Diagram of longitudinal section through tip of finger to show development of nail, as in a fetus of the fifth month The nail shown in black, begins to grow at the base, and elongates by growing toward the tip of the finger under the eponychium

a thickening of the epithelium exists at the distal end of the nail area, known as the sole plate, which probably corresponds to the thickened epidermis of the foot pads of clawed animals (Fig 77)

C THE HAIR

The hair shaft is a derivative of the ectodermal layer of the skin, and the root includes both ectodermal and mesodermal parts The hairs begin to develop first as solid ingrowths of ectoderm, extending obliquely into the underlying mesodermal layer (Fig 78A) These ectodermal buds soon grow club-shaped and their deeper ends become indented to receive the dermal papillae (Fig 78B) The hair shaft arises as a specialization of the cells in the axial portion of the bud It begins to form at the base of the hair bud and grows outward through the surface The outer layer of the epidermal bud develops into the inner and outer sheaths, and the portion of the dermis surrounding it becomes modified as the connective tissue sheath (Fig 78C) The erector muscles of the hairs develop from mesenchyme near the hair roots

The first hair roots appear about the beginning of the third month on the eyebrows, upper lip, and chin The first hair shafts appear above the surface of the skin about the fourth month The earliest

hairs formed are very fine and are present in large numbers, forming a dense, fine growth over the entire body, known as lanugo. The lanugo is lost and replaced by coarser hairs during fetal life and early infancy, except on the face, where it persists as a scarcely noticeable down. Hairs are constantly shed and replaced during life.

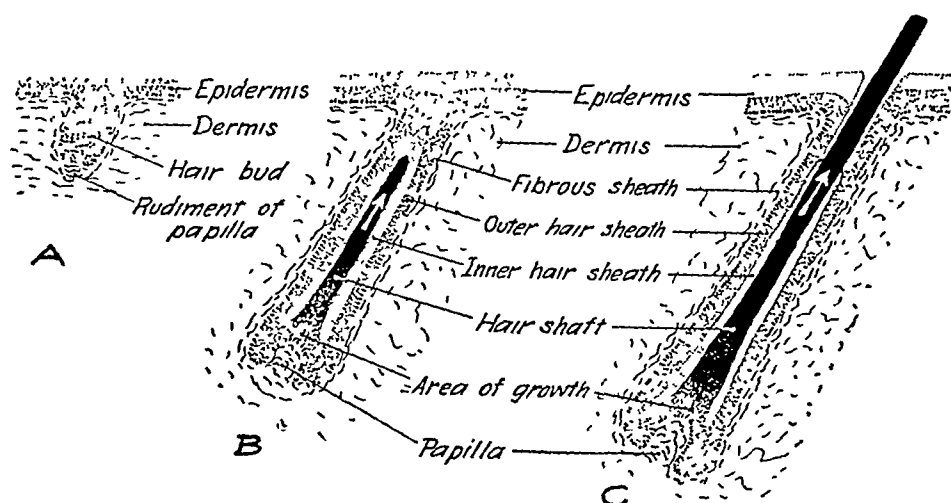


FIG 78. Diagrams showing the development of hairs. A, early stage of hair bud. B, the hair shaft has differentiated from the axial portion of the bud and is growing toward the surface. C, fully developed hair.

D. THE SEBACEOUS GLANDS

Nearly all the sebaceous glands develop in connection with hair follicles. They arise as solid buds, usually from the side of the ectodermal hair bud, less frequently from the epidermis itself. The central cells of the glands undergo fatty degeneration to form the secretion, after the manner of holocrine glands.

E. THE SUDORIFEROUS GLANDS

Sudoriferous glands arise as solid ingrowths of epidermal cells (ectoderm) into the underlying dermis during the fifth month (Fig. 79). Later the deeper part of the rudiment becomes coiled and the lumen appears (Fig. 79C). The cells of these epidermal rudiments become differentiated into two layers, the inner epithelial layer and the surrounding smooth muscle fibers.

F. THE MAMMARY GLANDS

The mammary glands are considered to be modified sweat glands, to which they have a quite similar development. The first rudiments

of the mammary glands are the two milk lines. Each milk line is a thickened ridge of ectoderm extending between the bases of the

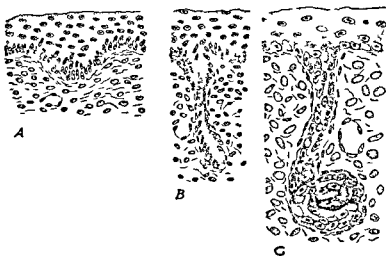


FIG 79 Three stages in the development of sudoriferous or sweat glands (Redrawn from Kollmann's *Handatlas*)

anterior and posterior limb buds. They make their appearance about the sixth week (Figs 80 and 81A). All the milk line disappears except

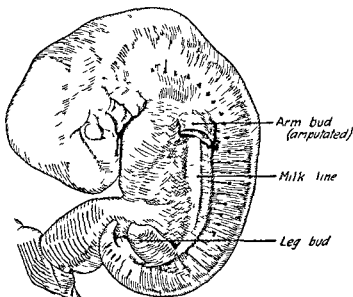


FIG 80 Human embryo 135 mm long (about 6½ weeks), showing the milk line (Redrawn from Kollmann's *Handatlas*)

a short portion in the pectoral region, where its ectoderm grows downward into the underlying mesenchyme. This ingrowth of ectoderm later becomes branched, develops a lumen, and becomes differentiated

into the epithelium and smooth muscle of the alveoli of the mammary glands (Fig. 81*B*). The fibrous portion of the glands develops from the mesenchyme of the developing dermis. The nipple is at first depressed (Fig. 81*B*) but becomes elevated about the time of birth. At birth the glands are about equally developed in both sexes, and they continue to develop about equally till the time of puberty, when

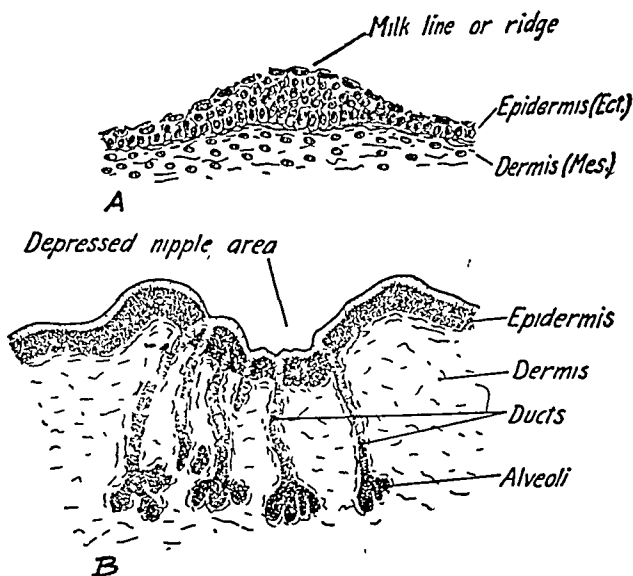


FIG. 81. Two stages in the development of the mammary gland, as seen in sections through the skin. *A*, section through the milk line of an embryo like the one shown in Fig. 80. *B*, through mammary gland of advanced fetus, showing the depressed nipple area and the primitive alveoli and their ducts. (Redrawn from Kollmann's *Handatlas*.)

rapid development takes place in the female. The development of the female mammary glands at puberty consists chiefly in growth of supporting tissue and adipose, though some proliferation of the epithelial glandular tissues occurs. Not until pregnancy does the glandular epithelium undergo great development.

G. THE VERNIX CASEOSA

The skin of the newborn child is covered, especially in the creases, with a pasty substance known as the vernix caseosa. It consists of the secretion of the sebaceous glands, desquamated epithelial cells, and hairs from the lanugo. Portions of this material are also found floating in the amniotic fluid.

H. ANOMALIES

An excessive development of the horny layer of the epidermis is known as ichthyosis, which in extreme cases gives rise to horny plates

separated by flexible sutures. Deficiency of pigment (albinism), affecting also hair and eyes, is an inherited condition. The common purple or red birthmark, known as hemangioma, is an excessive development of vascular channels in the dermis. Dermoid cysts are sometimes found along or near lines of fusion, as of branchial grooves, and are due to the inclusion of pieces of ectoderm at places where no ectoderm belongs. Excessive development of hair, general or local, is known as hypertrichosis and is believed to be an excessive and persistent growth of lanugo. Extensive or complete absence of hair is not so common and is usually associated with defective teeth and nails.

It is of interest to note that the milk line is present in the embryos of all mammals and that appropriate parts persist to produce the few or many mammary glands in positions characteristic of each species. In human beings of both sexes, supernumerary mammary glands of small size are by no means uncommon. They develop from various parts of the milk line and are found along a line extending from the axilla to the groin.

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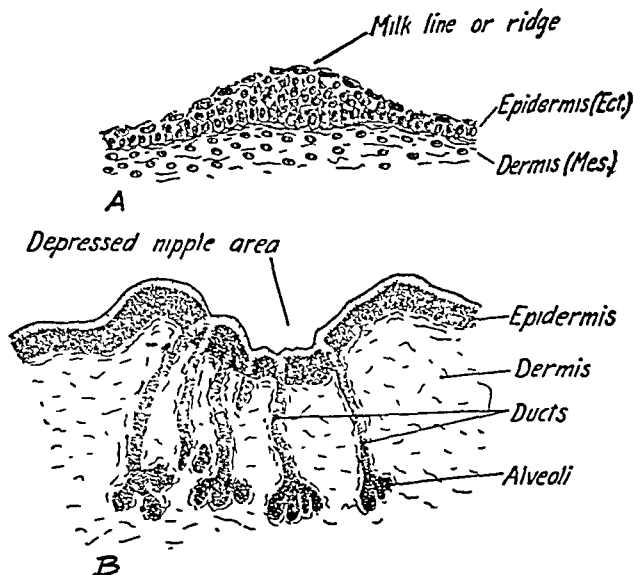


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stage The primitive gut as thus formed is a tube composed of entoderm The mesoderm surrounding it also plays an important part in the formation of the alimentary canal

The anterior end of the primitive gut very early expands into a cavity known as the pharynx The lateral walls of the pharynx show externally five vertical ridges, the branchial arches, separated by the narrow branchial grooves (Figs 21 to 24, pp 44 to 46) The branchial arches are also visible within the pharyngeal cavity, and between them, corresponding to the external grooves, are lateral extensions of the pharyngeal cavity, the branchial pouches (Fig 85) The entoderm of each of the four pouches comes into contact with the ectoderm of the corresponding groove, but they do not normally become perforated in the human embryo The amount of mesoderm in the arches is considerable, furnishing material for muscles, cartilages, bones, blood vessels, and other parts The embryonic human pharynx corresponds to the pharynx of fishes with its gills and gill slits Many

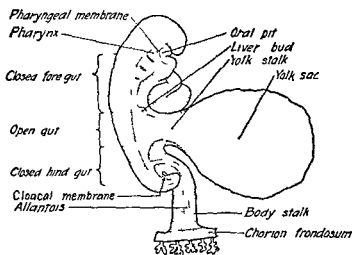


FIG 82 Outline of human embryo 26 mm long (4 weeks), showing the form and position of the embryonic gut This is like the embryo shown in Fig 21

important structures develop from it

The entodermal gut is at first without external openings (mouth or anus), which develop in the manner described on pp 41 to 43

The Oral Fossa

The oral fossa is a pit-like depression bounded above by the nodding fore brain, below by the mandibular process of the first arch, and on the sides by the maxillary processes (Figs 22, p 45, and 86A) It represents in a general way the oral cavity of the adult (Figs 27 to

CHAPTER XI

THE ALIMENTARY SYSTEM

The alimentary and respiratory systems are so closely related in their development, as well as in their adult relations, that it is impossible to describe either one without dealing to some extent with parts of the other. In function, also, they are closely related, both having the duty of supplying materials necessary for the activities of the body. These organs do not function before birth, because necessary food and oxygen are supplied through the digestive and respiratory organs of the mother by way of the placenta and the maternal and fetal blood vessels. Immediately at birth, however, the respiratory organs must begin to function, and the digestive organs shortly after; they must be ready or the child cannot live after birth.

In this chapter the development of some of the ductless glands will also be described, because they develop in connection with the alimentary tract.

A. EMBRYONIC PRIMORDIA OF THE ALIMENTARY SYSTEM

The cavity of the alimentary canal is derived from three embryonic cavities, the entodermal gut, the oral fossa (stomodeum), and the anal fossa (proctodeum).

The Entodermal or Primitive Gut

The mode of origin of the entodermal gut has already been described in connection with the development of the external form of the embryo and the fetal membranes. It was then seen that, when the embryo is formed by the folding of the embryonic disc, the upper part of the yolk sack is separated as the entodermal gut (Fig. 17). The gut is formed first in the anterior region of the embryo, where it is known as the fore gut, and later in the posterior region, where it is known as the hind gut. Between these two portions is the part which for a time remains in communication with the yolk sac through the yolk stalk (Fig. 82). The yolk stalk becomes relatively smaller and smaller, as the enclosure of the gut progresses (Figs. 21 to 24, pp. 44 to 46), and normally loses its connection with the gut at about the 9-mm.

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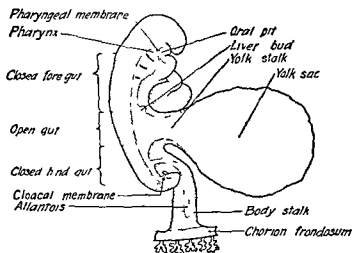


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partially illustrated in Fig 83C The epithelium of the alimentary canal is a direct derivative of the entoderm, which gradually takes on the characteristics of the various divisions of the digestive tract All the other layers come from the splanchnic mesoderm which now surrounds the entoderm The outermost layer of this mesoderm is the mesothelium, from which develops the mesothelial layer of the peritoneal or serous covering of the alimentary canal Between this

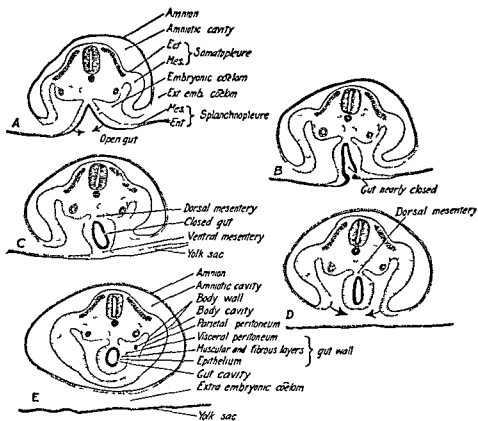


FIG 83 Drawings to show the origin of the body wall and alimentary canal Semidiagrammatic sections through the hind gut of a 72-hour chick embryo with the allantois omitted Section A is the most anterior, E the most posterior in the series

layer and the entoderm is a thick layer of mesoderm (mesenchyme), from which the muscles of the gut, including the circular and longitudinal layers and the muscularis mucosae, are derived The layer gives rise also to all the connective tissue of the gut, such as the submucosa, the tunica propria of the mucous membrane, and the connective tissue among the muscles and in the peritoneal layer

The numerous small glands in the wall of the digestive tube, such as the fundic and pyloric glands in the stomach and Lieberkuhn's

30, pp. 48 to 50). The oral pit is separated from the pharynx only by the thin pharyngeal membrane composed of ectoderm and entoderm (Figs. 85A and 117A, p. 165). The pharyngeal membrane breaks through in embryos about 3 mm. long (four weeks), thus producing the oral opening of the alimentary canal (Fig. 85B). Further details are given on pp. 126 to 129.

The Anal Fossa

A similar but shallower pit, the anal fossa or pit, forms opposite the posterior end of the primitive gut and is likewise separated from the entodermal part of the gut by the cloacal membrane (Figs. 82, 96, and 117A, p. 165).

With the breaking of the cloacal membrane the alimentary canal is established as a tube with two openings, lined for the greater part with entoderm, but for a short distance at each end with ectoderm. From this tube and the surrounding mesenchyme develop not only the alimentary canal and its glands but also the respiratory system and several other structures in no way connected with either digestion or respiration, most of which will be treated in this chapter.

B. HISTOGENESIS OF THE DIGESTIVE SYSTEM

The Alimentary Canal

The primitive gut is formed in the following manner. The two sides of the splanchnopleure fold inward and fuse ventrally, the entoderm forming the lining of the cavity and the mesoderm forming the other layers of the gut wall (Fig. 83). As the gut forms by the folding process, the right and left coelomic cavities unite with each other below the gut, because the ventral mesentery in the region caudad to the umbilicus disappears almost as soon as it is formed. The dorsal mesentery, however, persists from end to end, suspending the gut tube from the dorsal wall (Fig. 83). The complete wall of the alimentary canal is thus formed from the entodermal tube together with the splanchnic mesoderm of the coelom which has come to surround it.

The series of drawings in Fig. 83 illustrates not only the formation of the gut wall but also the fusion of the right and left parts of the somatopleure to form the ventral body wall which encloses the body cavity. Figure 84 pictures a section through a young human embryo showing the open gut and associated structures at a stage corresponding approximately to that in Fig. 83A.

The different tissues and layers of the adult alimentary canal are formed from the primitive gut tube as follows, the process being

partially illustrated in Fig 83C The epithelium of the alimentary canal is a direct derivative of the entoderm, which gradually takes on the characteristics of the various divisions of the digestive tract All the other layers come from the splanchnic mesoderm which now surrounds the entoderm The outermost layer of this mesoderm is the mesothelium, from which develops the mesothelial layer of the peritoneal or serous covering of the alimentary canal Between this

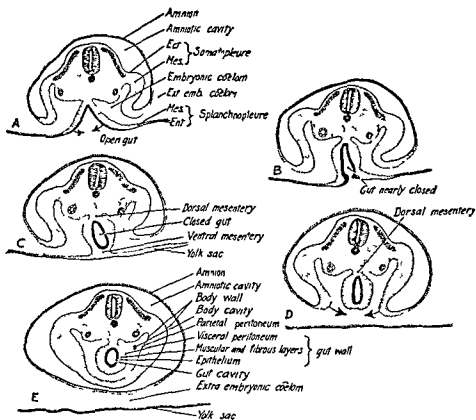


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The numerous small glands in the wall of the digestive tube, such as the fundic and pyloric glands in the stomach and Lieberkühn's

and Brunner's glands in the intestine, arise as growths of the entoderm into the mesodermal layer. Such structures as folds and villi arise as elevations which grow above the general surface and involve both entoderm and mesoderm.

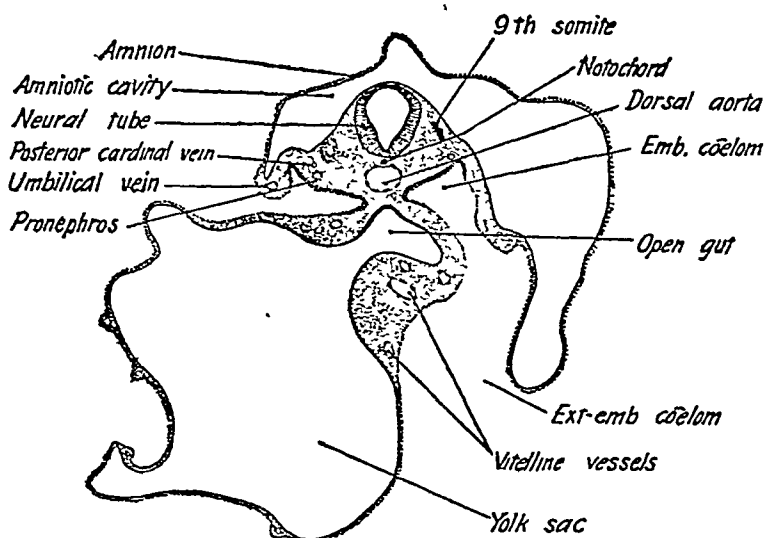


FIG. 84. Section through a human embryo 2.4 mm. long (about 4 weeks), corresponds to Fig. 83A. (Redrawn from Johnson in *Cont. to Emb.*, Carnegie Inst., Washington.)

The Larger Glands

Various sets of glands, such as salivary glands, thyroid, parathyroid, pancreas, and liver, arise as outgrowths from the alimentary canal. All such structures have their beginnings as buds which grow from the entoderm of the primitive gut or the ectoderm of the oral pit into the surrounding mesenchyme just as, in Chapter X, the glands of the skin were seen to start as buds of ectoderm (Figs. 79 and 81). These buds, in the larger compound glands, become very much branched, thus giving rise to the epithelium of the complicated duct system and the many alveoli of such glands. Some of these buds are, at the beginning, hollow, containing extensions of the lumen of the gut tube, whereas others are solid, the lumen developing at a later time. In the ductless glands (for example, the thyroid) the epithelial buds lose their connection with the parent tube, but in glands with ducts these connections persist as the ducts of the glands.

C. MORPHOGENESIS OF THE DIGESTIVE SYSTEM

The Oral and Nasal Cavities

The adult mouth, nasal cavities, and pharynx develop from the embryonic oral pit, nasal pits, and pharynx. These adult cavities

therefore are lined partly with ectoderm and partly with entoderm. It is not possible to locate exactly in the adult the position that corresponds to the embryonic pharyngeal membrane, but in the mouth

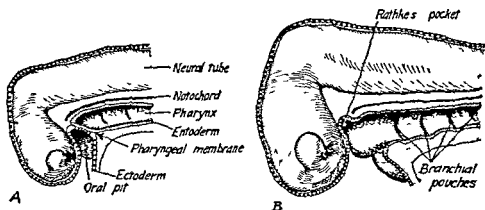


FIG 85 Diagrams of longitudinal sections through the pharynx of human embryos showing the condition both before and after the disappearance of the pharyngeal membrane (As pictured by His)

it is approximately at the anterior palatine arch, and in the nasal cavity at about the posterior edge of the nasal septum. In front of this membrane the epithelium is ectodermal, back of it entodermal (Figs 85 and 89).

At this point the mode of development of the face, as presented in Chapter V and illustrated in Figs 27 to 31, pp 48 to 50, should be well in mind, especially the parts played by the naso-frontal process and the maxillary and mandibular processes in the formation of the jaws and the external part of the nose. A knowledge of these matters is essential to an understanding of what is now to be presented.

The nasal pits begin to form in embryos about 4 mm long (four and one-half weeks) as a pair of ectoderm-lined depressions at the upper margin of the oral pit (Figs 27, p 48, and 86A). As the pits grow deeper, they soon assume the form of grooves extending inward in the roof of the oral pit between the median and lateral nasal processes (Fig 86A). Before long, fusion between the median and lateral nasal processes converts the pits into blind pouches which open externally by the external nares but have no internal communication with the oral pit (Fig 86B). About the same time the maxillary processes unite with the median nasal processes to complete the front margin of the upper jaw (Fig 86B). Shortly afterward the inner ends of the nasal pits rupture, establishing communication with the oral pit through the primitive internal nares. The nasal pits thus become the primitive nasal cavities, through which there is communication

and Brunner's glands in the intestine, arise as growths of the entoderm into the mesodermal layer. Such structures as folds and villi arise as elevations which grow above the general surface and involve both entoderm and mesoderm.

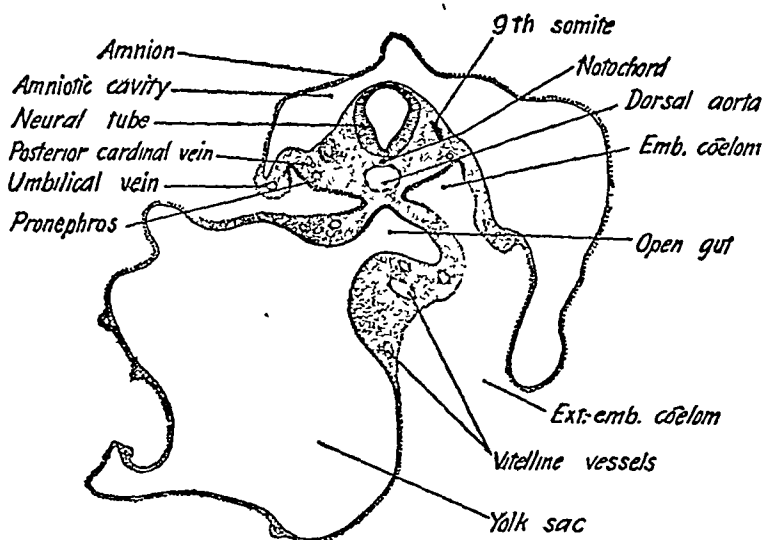


FIG. 84. Section through a human embryo 2.4 mm. long (about 4 weeks), corresponds to Fig 83A. (Redrawn from Johnson in *Cont. to Emb.*, Carnegie Inst., Washington.)

The Larger Glands

Various sets of glands, such as salivary glands, thyroid, parathyroid, pancreas, and liver, arise as outgrowths from the alimentary canal. All such structures have their beginnings as buds which grow from the entoderm of the primitive gut or the ectoderm of the oral pit into the surrounding mesenchyme just as, in Chapter X, the glands of the skin were seen to start as buds of ectoderm (Figs. 79 and 81). These buds, in the larger compound glands, become very much branched, thus giving rise to the epithelium of the complicated duct system and the many alveoli of such glands. Some of these buds are, at the beginning, hollow, containing extensions of the lumen of the gut tube, whereas others are solid, the lumen developing at a later time. In the ductless glands (for example, the thyroid) the epithelial buds lose their connection with the parent tube, but in glands with ducts these connections persist as the ducts of the glands.

C. MORPHOGENESIS OF THE DIGESTIVE SYSTEM

The Oral and Nasal Cavities

The adult mouth, nasal cavities, and pharynx develop from the embryonic oral pit, nasal pits, and pharynx. These adult cavities

maxillary processes until they meet and fuse in the mid line, forming a horizontal partition, the palate (Figs 87 and 88) This fusion begins at the front and progresses inward, subdividing the oral pit and the anterior end of the pharynx into a dorsal portion, the nasal cavity, and a ventral portion, the oral cavity (Fig 89)

Meanwhile the nasal septum has been developing as an extension of the naso-frontal process into the part of the oral pit above the developing palate (Fig 88) Separation of right and left nasal cavities is completed by fusion of the ventral margin of the septum with the palate The septum extends inward as far as the deeper end of the oral pit but does not extend into the pharynx, thus leaving the nasopharynx undivided The complete nasal cavities are thus formed by adding a portion of the oral pit to each of the primitive nasal cavities There is no definite limiting landmark in the adult between these two parts of the nasal cavities, but the dividing line roughly extends from

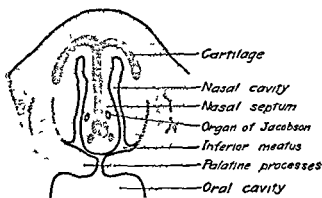


FIG 88 Section through head of human embryo 28 mm long (about 8 weeks), showing the condition when the nasal septum and the two palatine processes are just about to unite (Redrawn from Peter in Hertwig's *Handbuch*)

the nasal end of the incisive canal upward and backward to the antero-inferior angle of the sphenoid bone, the part from the primitive nasal pits forming the major portion of the nasal cavities (Fig 89)

While the palate and the nasal septum are being formed as described above, the nasal septum and the lateral walls of the nasal cavities grow rapidly, with the result that the jaws recede from the base of the skull, and the two nasal cavities (except at the external nares) become high, narrow slits instead of the earlier small passages

The nasal conchae develop from folds which grow out from the lateral walls of the nasal cavities, whereas the several paranasal sinuses develop as hollow growths from the nasal cavities into the surrounding mesenchyme

between the external nares and the oral pit, as indicated by the arrow in Fig. 87.

The wall between the two nasal cavities is formed by the naso-frontal process, which has now become the primitive nasal septum.

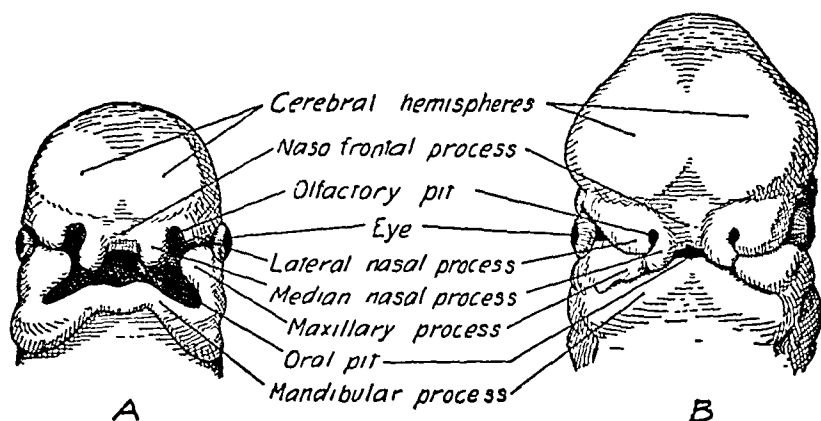


FIG. 86. Front view of face of two human embryos, especially to show the mode of formation of the external nostrils, the nasal septum, and the front margin of the upper jaw. A, embryo 8 mm. long. (After His.) B, embryo 11.3 mm. long. (After Rabl.)

The primitive septum is the anterior (external) part of the complete septum, which has not yet formed. The ventral end of the naso-frontal process gives rise to the philtrum of the upper lip and to the portion

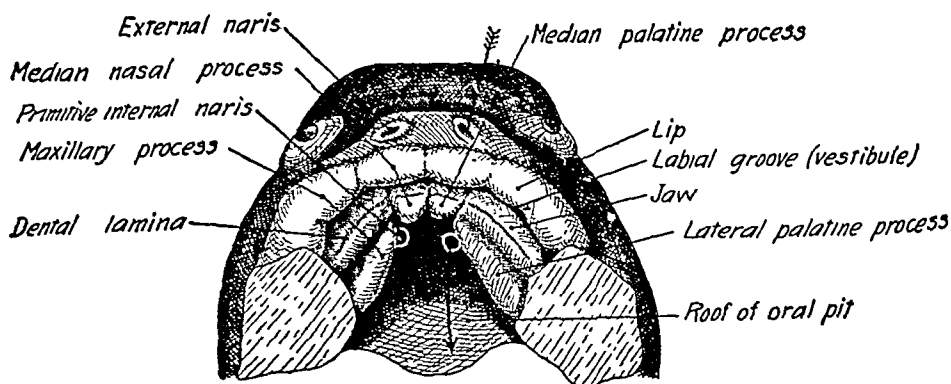


FIG. 87. Roof of mouth of human embryo two months old. Shows the development of the palate and labial groove, and the position of the dental lamina. The arrow passes through one of the primitive nasal passages. (As pictured by His.)

of the maxillary bone bearing the incisor teeth (the premaxilla or incisive bone, which remains separate in some mammals) (Fig. 87).

The main portion of the palate begins its development as a pair of shelves, the lateral palatine processes, which grow inward from the

maxillary processes until they meet and fuse in the mid line, forming a horizontal partition, the palate (Figs 87 and 88) This fusion begins at the front and progresses inward, subdividing the oral pit and the anterior end of the pharynx into a dorsal portion, the nasal cavity, and a ventral portion, the oral cavity (Fig 89)

Meanwhile the nasal septum has been developing as an extension of the naso-frontal process into the part of the oral pit above the developing palate (Fig 88) Separation of right and left nasal cavities is completed by fusion of the ventral margin of the septum with the palate The septum extends inward as far as the deeper end of the oral pit but does not extend into the pharynx, thus leaving the nasopharynx undivided The complete nasal cavities are thus formed by adding a portion of the oral pit to each of the primitive nasal cavities There is no definite limiting landmark in the adult between these two parts of the nasal cavities, but the dividing line roughly extends from

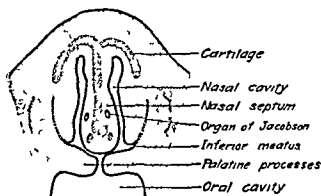


FIG 88 Section through head of human embryo 23 mm long (about 8 weeks), showing the condition when the nasal septum and the two palatine processes are just about to unite (Redrawn from Peter in Hertwig's *Handbuch*)

the nasal end of the incisive canal upward and backward to the antero-inferior angle of the sphenoid bone, the part from the primitive nasal pits forming the major portion of the nasal cavities (Fig 89)

While the palate and the nasal septum are being formed as described above, the nasal septum and the lateral walls of the nasal cavities grow rapidly, with the result that the jaws recede from the base of the skull, and the two nasal cavities (except at the external nares) become high, narrow slits instead of the earlier small passages

The nasal conchae develop from folds which grow out from the lateral walls of the nasal cavities, whereas the several paranasal sinuses develop as hollow growths from the nasal cavities into the surrounding mesenchyme

The vestibule of the mouth is formed by the ingrowth of a sheet of ectoderm into the mesoderm along the edge of each jaw, thus dividing it into an inner part bearing the teeth and an outer part, the lip. This sheet of ectoderm later splits, forming the cavity of the vestibule, which separates the lips and cheeks from the dental arches and gums (Fig. 87).

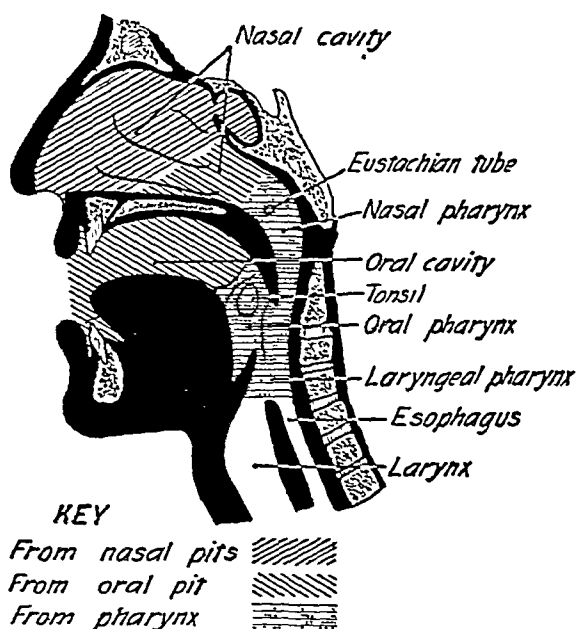


FIG. 89. Mid-sagittal section through adult face, shaded to show the parts played by oral pit, nasal pits, and pharynx in the development of the oral and nasal cavities.

In the following paragraphs will be described several small organs which develop as specializations of the lining of the oral and nasal cavities, some of them being derived from the ectoderm of the oral pit and others from the entoderm of the pharynx.

Derivatives of the Oral Pit

The Teeth. The enamel of the teeth is derived from the ectoderm, the dentine and the cement from mesoderm.

The Enamel. The enamel is a secretion of the enamel organ, which forms as follows. In embryos of about six weeks a sheet of ectoderm, the dental lamina, grows into the mesenchyme along the edge of the jaw in the position which the teeth will occupy. Figure 87 shows the position of the dental lamina on the surface of the jaw. From this lamina there arise in each jaw ten cup-shaped structures with the concavity directed away from the surface of the jaw. These are the enamel organs for the decidual or milk teeth. Figure 90 shows one of

the enamel organs in a section of the jaw. The enamel organs soon lose their connection with the ectoderm covering the jaw.

About the ninth week the enamel organs have become definitely formed, and in the concavity of each is a dense mass of mesenchyme, the dental papilla (Fig 90). The main mass of each enamel organ is composed of enamel pulp, a loose ectodermal tissue resembling mesenchyme, and its outer (convex) surface is covered with the thin, outer enamel cells. The concave surface of the organ, which faces the dental papilla, is formed by the inner enamel cells, which are columnar cells known as ameloblasts. The ameloblasts secrete the enamel, layer after layer, between themselves and the dental papilla (Fig 91), each ameloblast producing one enamel prism. After the full amount of enamel has been produced, the enamel organ degenerates.

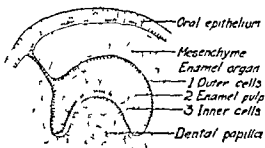


FIG 90 Diagram of section through jaw of embryo showing tooth germ and its relation to both oral epithelium (ectoderm) and mesenchyme (mesoderm)

The Dentine The outer cells of the dental papilla become columnar and are known as odontoblasts, because they secrete the dentine. The production of dentine begins slightly before the secretion of enamel, and from the relation between the enamel organ and the dental papilla it can readily be seen that the enamel will be secreted in the form of a cap over the dentine (Fig 91). Each odontoblast has a branched process which extends into one of the dentinal canals and grows longer as the thickness of the dentine increases (Fig 92). The part of the dental papilla inside the odontoblast layer becomes the dental pulp, the so-called nerve, which fills the root cavity. The amount of pulp becomes less and less as the dentine grows thicker. The formation of dentine and enamel of the deciduous teeth begins early in the fifth month and of the first permanent molars during the sixth month. In the other permanent teeth dentine and enamel do not begin to form until after birth.

The Cement (Cementum) The mesenchyme surrounding the embryonic tooth gives rise to the dental sac (Fig 91). The innermost cells of the dental sac become osteoblasts, which lay down on the outside of the dentine (but not over the enamel) a layer of bone, the cement, which forms the outer layer of the root of the tooth. The thin portion of the dental sac that remains after the tooth attains its full growth becomes the periodontal membrane, the common layer of

periosteum between the tooth and the bony socket surrounding it, which serves to hold the tooth in place.

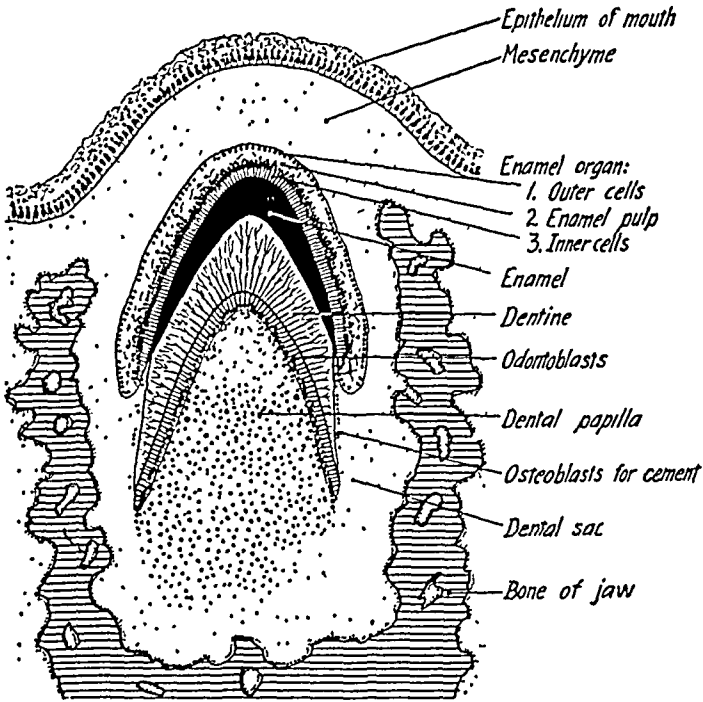


FIG. 91. Diagram of developing tooth, showing how enamel and dentine are deposited.



FIG. 92. Five odontoblasts from newborn cat, secreting dentine. (After Prenant, in Lewis and Bremer, *Text-book of Histology*, P. Blakiston's Son & Co., Philadelphia.)

The Growth and Eruption of the Teeth.

The early development of the tooth takes place while it is embedded in the tissue of the jaw. In this position the growth of the enamel is completed, and the enamel organ degenerates. The dentine and cementum, however, continue to grow for a longer time, and it is their growth at the root of the tooth that pushes it up through the gum; but their growth, too, is limited, and after complete eruption the tooth does not increase in length.

It is of interest to note that teeth belong primarily to the skin, not to the skeleton. The development of the teeth suggests strongly that of hairs, ectoderm and mesoderm playing comparable parts in both. In the lower vertebrates (for example, the dogfish) the teeth are merely scales of the skin, and only in the higher groups do they become firmly attached to the jaw bones.

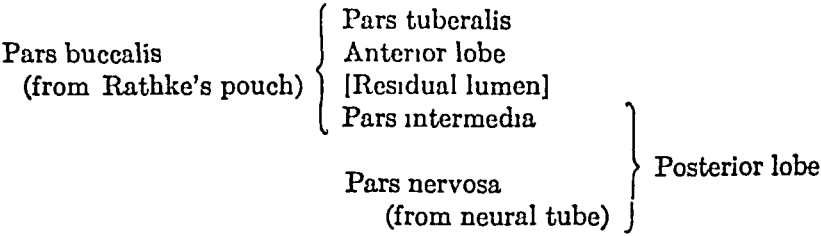
The Deciduous and Permanent Teeth The human deciduous teeth begin their development adjacent to the jaw bones but not within sockets or alveoli. The alveoli are formed by the development of the osseous alveolar process about the growing teeth. Moreover, when teeth are lost, the alveolar process surrounding the sockets is absorbed. The jaw bone of old age after the loss of the teeth resembles that of infancy before they form.

Inasmuch as teeth do not increase in size after eruption, the twenty small teeth of the child would be wholly inadequate for the larger jaws of the adult. The deciduous teeth are accordingly replaced by larger permanent teeth at the appropriate time, and twelve others also appear. The deciduous teeth erupt between the ages of six months and three years. They are shed between the seventh and twelfth years and are immediately replaced by the corresponding permanent teeth. Additional permanent teeth, enough to bring the number up to thirty-two, are erupted between the sixth and twenty-fifth years. The permanent teeth develop from rudiments which begin to form as early as the fourth month, when the enamel organs of some of them arise as buds from the dental lamina. The rudiments of all the permanent teeth are well formed before the loss of the milk teeth, and there is accordingly a time when all the teeth of both sets are represented in the jaw.

The Salivary Glands The epithelium of the salivary glands arises as outgrowths from that part of the mouth which develops from the oral pit, and hence is ectodermal. The parotid gland appears in embryos of about 8 mm (five and one-half weeks) as a solid growth of epithelium into the underlying mesenchyme at the angle of the mouth. As the epithelial growth penetrates more deeply into the underlying tissues, it branches richly, and finally the lumen appears in its various parts, forming the single duct with its many tributary ducts and terminal alveoli. The submaxillary gland has a development quite similar to that of the parotid, except that its rudiment arises in the groove between the tongue and the jaw. It appears in embryos about 11 mm long. The sublingual gland, which appears in embryos of about 24 mm, arises from several epithelial buds, instead of from one, as do the other salivary glands. Thus the sublingual gland with its several ducts embryologically corresponds to as many separate glands.

The Hypophysis The hypophysis (pituitary body) develops from two distinct primordia, both ectodermal. (1) The *pars buccalis* (mainly the anterior lobe) develops from Rathke's pouch, which arises as a hollow ectodermal outgrowth from the roof of the oral pit, beginning in embryos of less than 4 mm. From this pouch develop the

epithelial tissues of the gland. The lumen of the pouch becomes largely obliterated, and the stalk connecting the pouch with the oral pit degenerates. (2) The *pars nervosa*, which makes up the greater part of the posterior lobe, develops from a hollow outgrowth from the floor of the neural tube. It soon becomes a solid mass with the characteristic fibrous structure of this lobe. It retains its connection with the neural tube. The two parts of the gland very early become closely united. The developmental and adult relations may be expressed thus:



Derivatives of the Pharynx

The Tongue. Though the adult tongue occupies a position in the part of the mouth which is derived from the oral pit, the organ has its origin in the pharynx, from which position it grows forward into the floor of the mouth.

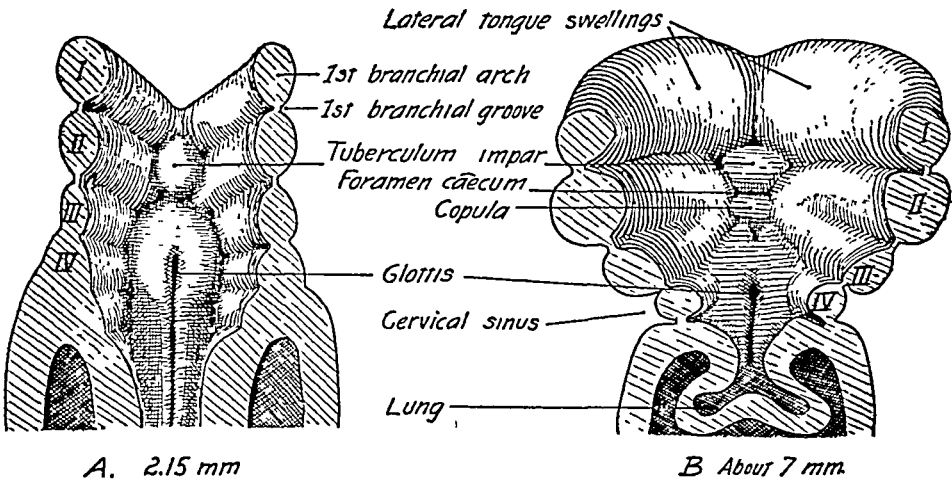


FIG 93. Ventral half of pharynx from the inside, showing rudiments of the tongue and other organs *A*, from embryo 2.15 mm long (about 4 weeks). *B*, from embryo 7 mm. long (more than 5 weeks). (After His.)

The earliest rudiment of the tongue is a swelling in the floor of the pharynx between the first and second arches, the *tuberculum impar*, which is present in an embryo 2.15 mm. long (less than four weeks) as shown in Fig. 93*A*. This rudiment forms only a small part of the tongue, located just in front of the *foramen caecum*, at the apex of the

V formed by the rows of circumvallate papillae (Fig 94B) The anterior end of the tongue develops from the lateral tongue swellings on the first arches (Fig 93B), which, as they increase in size, fuse in front of the tuberculum impar and grow forward to form the greater part of the tongue (Fig 94) The root of the tongue has its

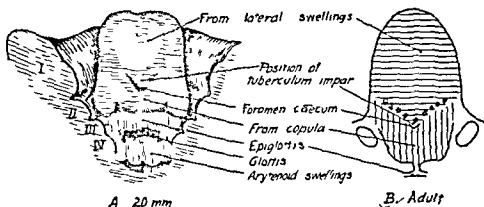


FIG 94 Two stages in the development of the tongue A, ventral half of pharynx in human embryo 20 mm long (more than 7 weeks) (After Kollmann) B, outline of adult tongue showing by differential shading the portions which come from anterior and posterior rudiments

origin from a median swelling, the copula, at the base of the second and third arches, just back of the tuberculum impar (Fig 93B) The epithelium of the anterior part of the tongue is derived from ectoderm; that of the posterior part from entoderm. The tongue musculature develops from mesenchyme in the floor of the pharynx, though its nerve supply, the hypoglossal nerve, suggests that phylogenetically it is derived from somites (see p 114)

The Thyroid Gland The thyroid gland is observed first in embryos of 3 mm as a median outpocketing of entoderm in the floor of the pharynx just caudad to the tuberculum impar (Figs 93 and 95) This outgrowth grows rapidly into the mesenchyme and soon separates from the pharynx. It is then carried caudad by the general growth process of the region. At the same time its lateral portions grow rapidly so that it becomes U-shaped, the lateral expansions destined to become the lateral lobes, and the median portion the isthmus. The point of origin on the floor of the pharynx is the foramen caecum. Thyroid follicles arise by the secretion of colloid in the center of small cell clusters.

The First Groove and Pouch The first groove becomes the external auditory meatus. The first pouch becomes the Eustachian tube and the tympanic cavity of the middle ear. The branchial membrane

separating the groove from the pouch becomes the tympanic membrane (Chapter XIX).

The Second Pouch; the Tonsils. The second pouches become flattened by growth expansion of the pharyngeal wall. They leave no

derivatives and no definite landmark in the adult. Late in the third month, however, the palatine tonsils begin to develop in the region formerly occupied by the pouches, but they are not considered derivatives of the pouches. The lymphatic tissue of the palatine tonsils arises from mesoderm. The pharyngeal tonsils (adenoids) develop similarly in the roof of the naso-pharynx.

The Third and Fourth Pouches. There are the following important derivatives of these pouches.

The Thymus Gland. In embryos about 6 mm. long a hollow outgrowth forms from the ventral aspect of each of the third pouches. These soon detach and become solid. They are carried caudad by differential growth. At the same

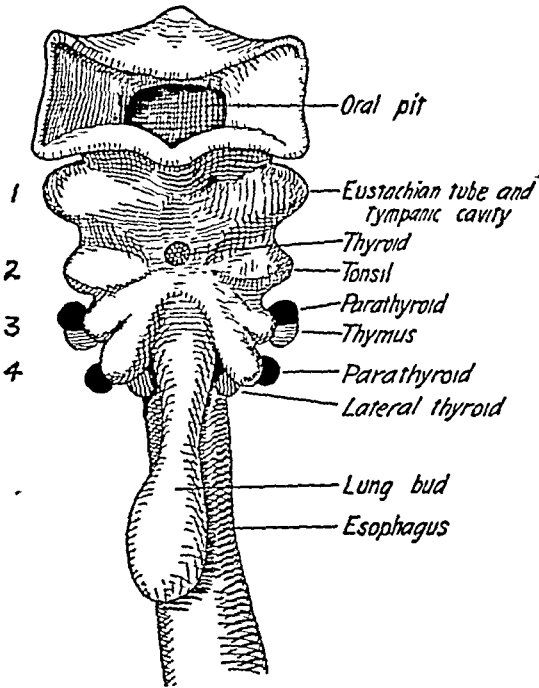


FIG. 95. Pharynx of human embryo 3 mm. long (about 4 weeks), as seen from the ventral side. The figure shows only the epithelial part (entoderm), with the surrounding tissues removed. Designed especially to show the origins of the various glands which arise from the pharynx (Redrawn from Kollmann's *Handatlas*.)

time they grow rapidly and soon meet and fuse in the mid line caudad to the thyroid. The mass continues its migration well into the anterior mediastinum of the thorax. Some of the entodermal cells form the reticulum, whose meshes become filled with thymic cells, and others become keratinized and concentrically flattened to form the thymic (Hassal's) corpuscles. The origin of the thymic cells is in dispute. Some workers, considering them to be of mesodermal origin, call them lymphocytes; others, believing that they are entodermal, prefer to call them thymocytes. The thymus reaches its greatest development at puberty, after which it undergoes an involution but apparently does not wholly disappear. The function of the thymus remains largely a problem for future investigation, the evidence for

an endocrine function being meager. Some workers believe that infrequently small masses of thymic tissue are also formed from the fourth pouches. Others hold the opinion that the cortex of the thymus, including the thymic corpuscles, develops from the ectoderm of the cervical sinus (see p 47).

The Parathyroid Glands Parathyroids III and IV arise as thickenings of the entoderm of the dorso-cephalic portions of the third and fourth pouches, respectively. They become detached and are carried caudad. Parathyroids III are carried farther than IV because for a time they are attached to the thymic primordia in their migration. The parathyroids become lodged on the dorsal surface of the thyroid.

The Ultimobranchial Bodies Evaginations from the caudo-ventral wall of the fourth pouch give rise to the ultimobranchial bodies (post-branchial bodies, lateral thyroids). They become detached, and along with parathyroids IV are carried to the dorso-median surface of the thyroid. Their exact fate is a matter of dispute, some investigators maintaining that they disappear, others that they produce thyroid material (hence the name, lateral thyroid).

The Digestive Canal (Exclusive of the Mouth)

The remaining divisions of the alimentary canal (esophagus, stomach, and intestine) are all much alike in their development, being derived from the primitive entodermal tube and the surrounding mesenchyme, as already described. The alimentary canal is suspended from the body wall by the dorsal mesentery (Fig 83E). At first the tube is approximately uniform in diameter throughout its length (Fig 96), but certain parts grow more rapidly than others, thus producing the enlargements that become the stomach and large intestine (Fig 110, p 157).

At first the alimentary canal has no pronounced curvature, except the general curvature of the embryo, but the tube grows in length more rapidly than the embryo. As a result it is thrown into elaborate coils. The lungs, liver, and pancreas arise as outgrowths from the tube at appropriate places. The yolk stalk and allantois also connect to it in early stages (Fig 96).

The Esophagus The esophagus is the part of the gut between the pharynx and the stomach. It does not undergo much enlargement, remaining as one of the smaller parts of the alimentary canal (Figs 96 and 110, p 157). It is at first very short but increases in length as differential growth carries the stomach caudad.

The Stomach The stomach appears as an enlargement of the gut, first evident in embryos of 4 to 5 mm (Fig 96). At the time of its

origin it lies well cephalad, but during its development it migrates caudad through about eight segments. The stomach is at first straight, but the dorsal side grows more rapidly than the ventral, thus producing the greater and lesser curvatures. At the same time the stomach is crowded toward the left side of the body, the liver occupying the right side. During the change of position the stomach rotates on its long axis so that the greater curvature (originally the dorsal

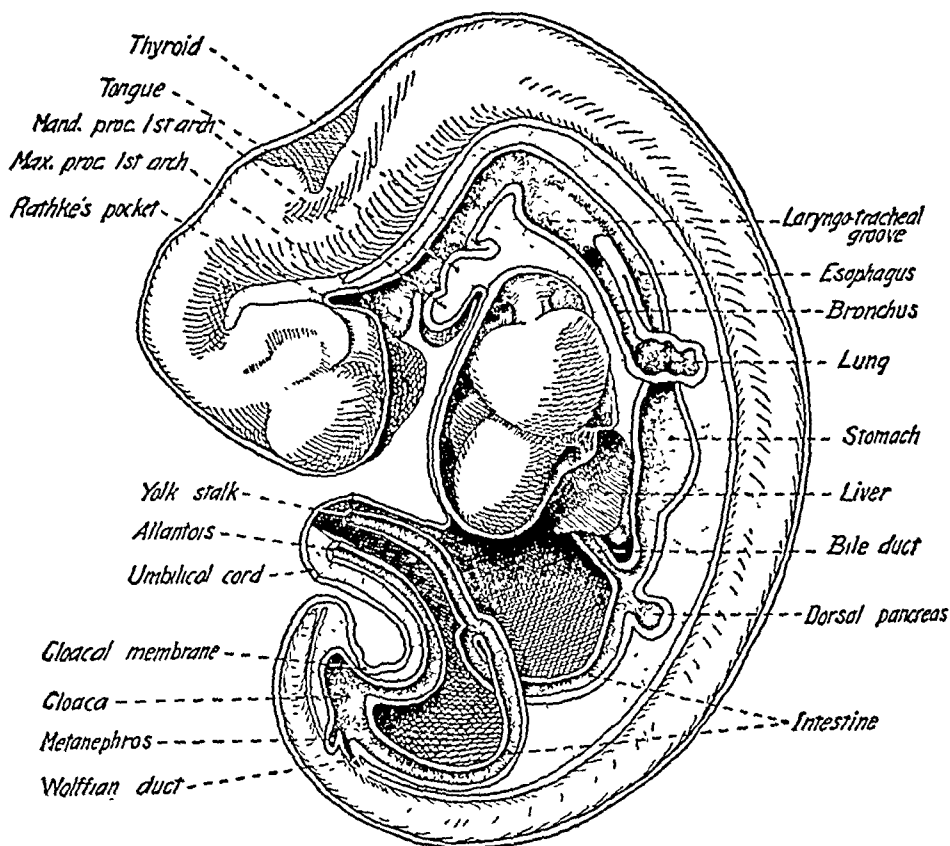


FIG. 96. Median dissection of a human embryo 5 mm. long (about 5 weeks) to show the general relations of the parts of the alimentary canal. (After His.)

surface) comes to face toward the left and caudad, whereas the lesser curvature faces in the opposite direction. The embryonic left side is now the ventral surface of the organ, and the right side has become the dorsal surface. This fact explains why the left vagus nerve supplies the ventral surface and the right nerve the dorsal surface of the organ. Figure 111, p. 158, shows in ventral views and in cross-sections the change in position of the stomach. The rotation of the stomach is a gradual process, beginning early in the sixth week and being practically completed by the end of the third month.

The Intestine In embryos of about 5 mm (five weeks) the intestine is a slender tube extending from the stomach to the posterior end of the body without marked curvature. Its posterior portion, the cloaca, is slightly enlarged and receives the mesonephric (Wolffian) ducts from the embryonic kidneys (Fig 96). From about the middle of the intestine arises the yolk stalk, which closes off during the sixth week. The allantois arises from the ventral side of the cloaca (Fig 96).

In embryos of 7 mm the terminal portion of the gut, the large intestine, begins to expand more rapidly than the part which becomes the small intestine. At the junction of these two parts an outgrowth forms, from which the cæcum and the vermiform appendix develop by differential growth (Fig 110, p 157). In the sixth week the intestine begins to elongate very rapidly and soon forms loops of increasing complexity which adapt it to the form of the body cavity in which it lies. At an early stage, when but a single U-shaped loop has been formed, this loop undergoes a torsion which brings the large intestine across in front of the duodenum and contributes to the formation of the characteristic curvature of the large intestine (compare Fig 1134, p 160, with Fig 110, p 157). In embryos of about seven weeks (19 mm) some of the coils of the growing small intestine expand into the part of the body cavity in the base of the umbilical cord, but by the close of the tenth week (40 mm) they have again withdrawn into the body.

The Rectum The rectum is formed by the division of the cloaca into dorsal and ventral portions by a transverse partition. The dorsal division is the rectum, and the ventral one is the urogenital part, the development of which will be described in Chapter XVII. This division is completed in embryos about 15 mm long (nearly seven weeks). The division of the cloaca also separates the cloacal membrane into two parts, the anal membrane and the urogenital membrane. The anal membrane ruptures in embryos about 30 mm long (nine weeks).

The Liver and Pancreas

The Liver The liver arises as a hollow outgrowth of entoderm from the mid-ventral line of the duodenal part of the gut, beginning in embryos of about 2.5 mm (four weeks) (Fig 82). It soon takes the form of a thick-walled vesicle. Solid anastomosing cords of cells grow out from this entodermal sac. The vesicle from which these cords arise develops into the gall bladder and the larger ducts, and the cords become the cords of liver cells in which develop the bile capillaries.

The liver rudiment grows out in such a place that it at once becomes embedded in the septum transversum, a mesenchymal partition across

the coelom (Figs. 103, 104A, and 106A, pp. 150 to 153). From the mesenchyme of the septum transversum is derived the capsule and all other fibrous parts of the liver.

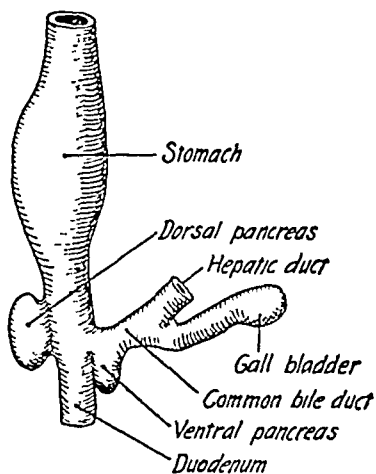


FIG. 97. An early stage in the development of the pancreas, showing its two rudiments. From embryo 7.5 mm. long (more than 5 weeks). (After Thwing in *Am. Jour. Anat.*)

An important point in the development of the liver is that when the liver bud grows out from the gut it lies close to the two vitelline veins (Figs. 103 and 104A, pp. 150 and 151), and that while the cords of liver cells are being formed the vitelline veins are breaking up into a plexus of small vessels, the sinusoids, which become interwoven with the developing liver cords. This subject is more fully treated in Chapter XIV.

The liver grows so rapidly that it soon occupies the greater part of the body cavity. It attains its maximum relative size in embryos of about 31 mm. (nine weeks), when it constitutes a little more than 10 per cent of the weight of the body. At birth it constitutes 5 to 6 per cent of the body weight, and in the adult about 2½ per cent.

The Pancreas. The pancreas arises from the duodenal part of the developing gut by two separate hollow outgrowths, beginning in

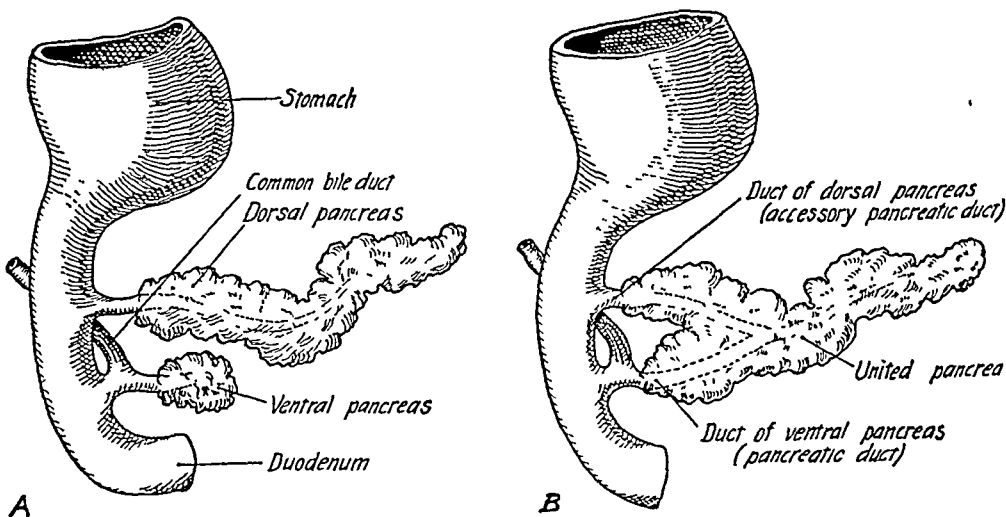


FIG. 98. Later stages in the development of the pancreas. (Redrawn from Kollmann's *Handatlas*.)

embryos of about 4 mm. (less than five weeks), one from the base of the liver rudiment and one from the dorsal surface of the

duodenum almost opposite it (Fig 97) The dorsal rudiment expands into the dorsal mesentery and grows more rapidly than the ventral It forms the greater part of the adult pancreas The two parts unite in embryos about 20 mm long (Fig 98) Before their union each part has its own duct, but after this union the ducts within the organ also unite The duct of the ventral portion soon becomes the main pancreatic duct, discharging through the base of the bile duct, and that of the dorsal part forms the smaller, accessory pancreatic duct, or sometimes loses its connection with the duodenum entirely

In the histological differentiation of the gland, the pancreatic islands, as well as the epithelium of the alveoli and ducts, are derived from the entodermal outgrowths, and the supporting portions come from the splanchnic mesoderm surrounding the entodermal gut

D ANOMALIES

The anomalies of oral and nasal passages, such as hare lip and cleft palate, have already been treated in Chapter VIII

The lower jaw is sometimes very small or wanting, because the mandibular process fails to develop In such cases the two external ears are united in the mid-ventral line

Anomalies of the teeth, including absence of some teeth or presence of additional ones, are common A defect in the enamel organ may cause the enamel to be wanting The tongue may be defective because of non-development of one or more of its parts or to incomplete fusion of these parts

The first branchial groove sometimes becomes permanently perforated to form a fistula from the pharynx opening just below the ear The second groove sometimes forms fistulas along the ventral margin of the sternocleidomastoid muscle In other anomalies, portions of the epithelium of some of the internal or external grooves become covered over and persist to form either entodermal or ectodermal cysts The thyro-glossal duct may persist in varying degrees, causing cysts

The esophagus is in rare instances reduced to a solid cord of cells and more frequently is occluded or has fistulous connection with the trachea The stomach may be somewhat reduced in size, even to the form of a small tube like the rest of the gut

The most common anomaly in the intestine is the persistence of the yolk stalk as Meckel's diverticulum, attached to the ileum about three feet from the cæcum At its greatest development it forms an umbilical fistula, but more often it is only a blind diverticulum about the size of the vermiform appendix Closure or constriction of the lumen of

the intestine sometimes occurs. Sometimes the cloaca fails to divide, giving rise to various sorts of anomalous relations between digestive and urogenital tracts. The anal membrane occasionally fails to rupture.

Congenital malformations of the liver are rare. Accessory pancreases in the wall of the intestine and the stomach, representing additional rudiments, are not uncommon. The duct of the dorsal pancreas may persist as a separate duct or, after the degeneration of the ventral duct, may serve the entire organ.

Situs inversus is a type of anomaly in which there is a reversal of asymmetry of viscera, those on the right side appearing on the left and vice versa. In complete cases, not only the digestive organs but also all the abdominal and thoracic viscera are reversed; the heart points toward the right and the aorta arches toward the right; the stomach is on the right and the liver on the left, and so for all the viscera. Usually the reversal is not complete, only certain organs being reversed. The cause of reversal is not clear. Sometimes, but by no means always, reversal occurs in one member of identical twins. It is hardly probable that every individual so reversed is the surviving twin of a pair.

CHAPTER XII

THE RESPIRATORY SYSTEM

The earliest primordium of the respiratory system is seen in embryos of about 2.5 mm (four weeks). At that time an external longitudinal groove forms, pushing inward on each side of the esophageal part of the entodermal gut immediately caudad to the pharynx, this is the beginning of a division into a dorsal digestive part and a ventral respiratory part. The lateral grooves increase in depth, and soon the respiratory part becomes separated from the digestive part except at the anterior end, where it communicates with the posterior end of the pharynx by the primitive glottis (Figs 93, 95, and 96). The distal (caudal) end of the respiratory part soon enlarges and then becomes bilobed, this division being already apparent in embryos of less than 5 mm (less than five weeks). The two branches represent the future lungs, the unbranched part, the trachea and larynx.

A THE LUNGS

In the development of the lungs from the two entodermal primordia, there are three rather distinct phases, *two prenatal* and *one postnatal*. The *earliest prenatal phase* is characterized by *growth* and *branching* of the entodermal tubes. Very soon two branches are thus produced on the left side and three on the right, these five branches corresponding to the future lobes of the two lungs (Fig 99). The branches continue to grow longer and to fork actively at their tips, until in the fifth month probably seventeen generations of branches (the complete prenatal number) have been formed. Thus an elaborate, tree-like system of entodermal tubes is produced for each lung.

These growing and branching entodermal tubes push out into the mesenchyme below the esophagus (the equivalent of a broad ventral mesentery) which in the region of the esophagus separates the right and left halves of the coelom and develops into the ventral mediastinum. This mesenchyme furnishes the supporting tissues of the lungs, and the blood vessels of the lungs develop in it. Each growing lung bud soon expands laterally into the adjacent coelomic space (the future pleural sacs), pushing ahead of it the superficial splanchnic mesoderm of the mesentery (Figs 99 and 105, p 152). The median

walls of the pleural sacs thus come to invest the growing lungs, forming the visceral pleura with its mesothelial covering.

The second prenatal phase of development is characterized by differentiation and expansion. At the sixth month the epithelium of

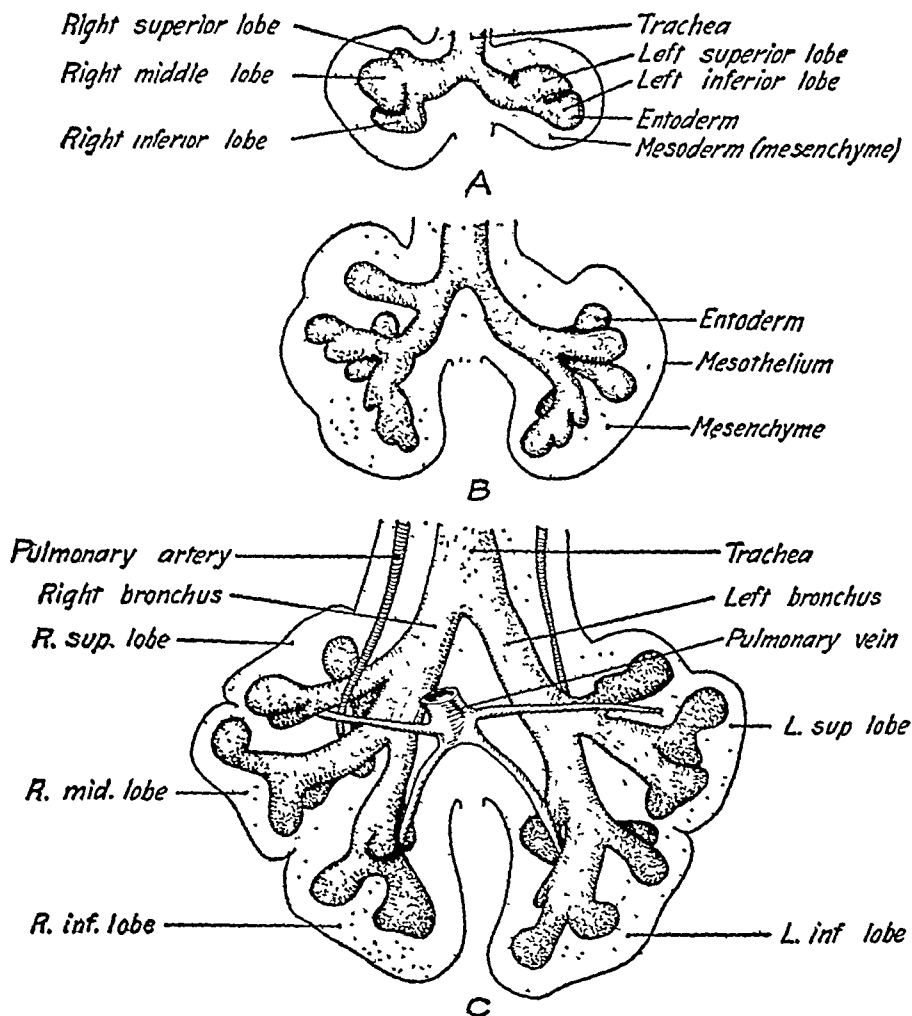


FIG. 99. Three stages in the development of the lungs. A, from embryo 4.3 mm. long (nearly 5 weeks). B, from embryo 8.5 mm. long (about 5½ weeks). C, from embryo 10.5 mm. long (6 weeks). (After His.)

the respiratory tree is columnar in the older generations and cuboidal in the younger, terminal segments. Between the epithelial tubes is much connective tissue, and the growing lung resembles a compound gland more than a lung. During the later prenatal months a more typical lung structure develops. In these months the terminal segments enlarge to form the respiratory air sacs (alveoli, alveolar sacs, and alveolar ducts). At the same time the connective tissue becomes

relatively less abundant and the expanding air sacs come close together, so that adjacent sides are mutually flattened and the air spaces are separated only by the thin alveolar walls, in which lies the rich network of respiratory capillaries

During this phase of development the epithelial lining of the air sacs undergoes significant changes, the exact nature of which is still a matter of doubt. Some writers believe that during the later fetal months the cuboidal epithelium becomes reduced to a very thin

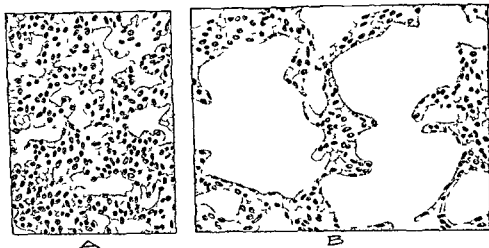


FIG 100 Two areas from lung of a child who died immediately after birth when lungs had been partially inflated. Both drawings to the same scale. A, Area which has not been inflated, illustrating condition of late fetal lung. B, Inflated area, showing condition immediately after the beginning of respiration.

squamous type, forming a respiratory epithelium which lines all the alveoli. Others, who are unable to find any epithelium lining the alveoli of the adult lung, maintain that the earlier epithelium wholly disappears. During this phase of development the older generations of the respiratory tree (bronchi and bronchioles) retain their tall epithelium, and from the intervening mesenchyme the other tissues of their walls develop. Just prior to birth, the lung tissue, though much less compact than at the middle of pregnancy, is still quite unlike that of the adult lung (Fig 100), but with the inspiration of air after birth, the air sacs become distended and within about three days assume almost the adult appearance.

After birth the *third phase of development* is accomplished. The growth of the lungs during infancy and childhood is attained not by enlargement of the air sacs, but by a *renewed branching* which brings about an increase in their number. The branching is accomplished by terminal sprouting from the alveolar sacs, these sprouts expanding into new generations of air sacs. Several generations of such postnatal

sprouts are produced. As the production of new air sacs thus goes on, there is no pronounced increase in the length of the thin-walled respiratory passages, inasmuch as some of the older generations become converted into bronchioles with taller epithelium, thus extending the conducting segments of the pulmonary tree at the expense of earlier respiratory segments. The respiratory bronchioles represent an incomplete stage in this transformation.

B. THE TRACHEA

The undivided portion of the entodermal respiratory tree, lying immediately ventrad to the esophagus, develops directly into the epithelium of the trachea. From the mesenchyme in which it lies, the supporting and muscular tissues of the tracheal wall, such as the cartilaginous rings, the connective tissue, and the trachealis muscle, develop. Inasmuch as the early primordium of the trachea lies in the thick septum (mesentery) which at that level separates the two sides of the coelom, the adult trachea lies in the mediastinum which develops from this septum.

C. THE LARYNX

The larynx arises from the proximal portion of the laryngo-tracheal tube, just at its attachment to the pharynx. The epiglottis is derived from the ventral portion of the third and fourth branchial arches. The swellings on the sides of the larynx which give rise to the vocal cords appear about the tenth week. The thyroid cartilage is derived from mesenchyme of the fourth and fifth branchial arches, whereas the cricoid and arytenoid cartilages arise from mesenchyme probably not associated with any of the arches.

D. ANOMALIES

The larynx may vary greatly in size, being either much too large or too small. The two lateral rudiments of the epiglottis may fail to fuse. The trachea is at times wanting, the bronchi connecting directly to the larynx. Variations in the lobulation of the lungs are quite common. As a rather frequent anomaly, the esophagus is divided transversely into two segments. The first arises normally from the pharynx but is merely a short sac which ends blindly. The second segment arises from the dorsal side of the trachea near its bifurcation and connects normally with the stomach. The only access to the stomach is thus through the trachea and this section of the esophagus. The condition is believed to originate in embryos of about 4 mm. by failure of the lateral grooves to separate fully and properly the digestive and respiratory parts of the primitive entodermal gut.

CHAPTER XIII

THE BODY CAVITIES

A. ORIGIN AND EARLY HISTORY OF THE CÆLOM

The cœlom of young human embryos includes two parts (1) the embryonic cœlom or body cavity, included within the body of the embryo proper, and (2) the exocœlom (extra-embryonic cœlom), which lies wholly outside the embryo (Figs 101 and 102). The pericardial, pleural, and peritoneal cavities of the adult are formed by subdivision of the embryonic body cavity.

The Extra-Embryonic Cœlom

In human development the exocœlom appears before the embryonic body cavity, in fact before the embryo begins to form from the embryonic disc. In implanted ova of eleven days the exocœlom is foreshadowed by the large area of loose extra-embryonic mesoderm (the *magma reticulare*), which lies inside the trophoderm and partly

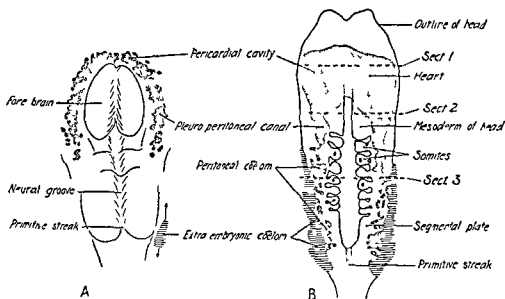


FIG 101 Projections of early cœlom as plotted from serial sections. Shows plan and mode of formation of embryonic cœlom by fusion of separate spaces. Adjacent region of exocœlom also shown. A, embryo of 1.5 mm (one somite) (Adapted from Davis). B, embryo of 2 mm (7 somites) (Adapted from Dandy). Sections at levels 1, 2 and 3 shown in Fig 102.

surrounds the developing amniotic cavity and yolk sac (Fig. 13, p. 35). During the third week of development, as pointed out in Chapter IV, this mesoderm largely disappears, leaving only the mesoderm of the chorion on the outer side and that of the amnion and yolk sac on the inner side (Figs. 14, 15, and 38, pp. 35, 37, and 62). Between these two layers lies the large extra-embryonic coelom. As the amnion expands it encroaches upon the exocoelom, which about the eighth week becomes entirely obliterated when the amnion comes into contact with the inner surface of the chorion (Fig. 38, p. 62).

The Embryonic Coelom (the Body Cavity)

The human embryonic coelom or body cavity arises independently of the exocoelom and somewhat later. It forms within the lateral, unsegmented mesoderm (lateral plate). It appears first about the middle of the third week as numerous small spaces in the lateral mesoderm in front of the head fold, where the two lateral plates have already united in the median line (Figs. 50, p. 79, and 101). These

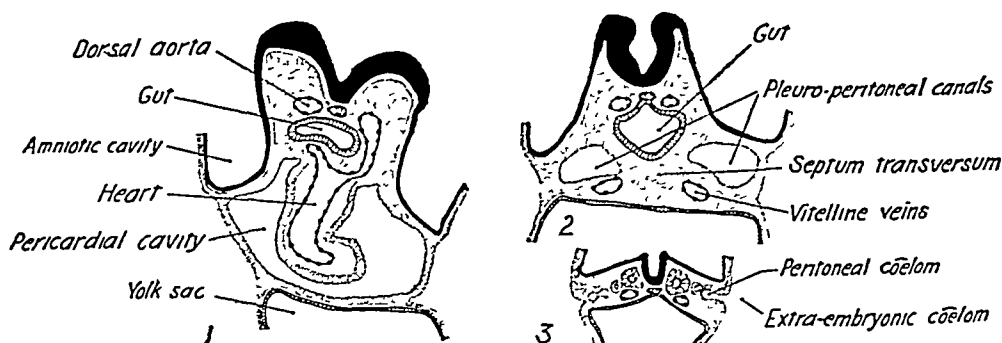


FIG. 102. Cross-sections through embryo of 2 mm, showing coelom. See Fig. 101 for levels of sections through pericardial cavity, pleuro-peritoneal canals, and peritoneal coelom. (Adapted from Dandy.)

spaces unite to form progressively larger spaces, and by the end of the third week a \cap -shaped coelomic cavity has formed (Fig. 101A). The most anterior part of the early coelom, at the bend of the \cap , is the pericardial cavity; the two lateral parts are the pleuro-peritoneal canals. Continued extension of the coelom on each side soon produces the beginning of the peritoneal coelom (Fig. 101B). The developing coelom separates each mesodermal plate into somatic and splanchnic layers, and before long the embryonic coelom becomes continuous with the earlier exocoelom (Figs. 84, p. 126, 101, and 102). As was pointed out in Chapter VII, the somatic and splanchnic layers of meso-

derm, together with the adjacent ectoderm and entoderm, form respectively the somatopleure (body wall) and splanchnopleure (gut wall)

B GENERAL RELATION OF BODY CAVITY TO GUT, LUNGS, AND HEART

The two lateral coelomic spaces do not for a time coalesce to form a single coelom, except in the pericardial region. In fact, the two remain separate until the yolk sac (splanchnopleure) folds to form the gut wall. As part of this folding process, the two coeloms approach each other, their bounding walls above and below the entodermal gut tube forming the dorsal and ventral mesenteries (Fig 83, p 125). The dorsal mesentery persists throughout its length, but the ventral mesentery caudad to the umbilicus immediately breaks down, allowing coalescence of the right and left coelomic cavities to form a single body cavity (Fig 83C, D, E).

The lining of this early coelomic cavity gives rise to the mesothelial lining of the large cavities of the body — peritoneal, pleural, and pericardial. In each of these cavities the serous membranes have the three parts, parietal, visceral, and supporting (Fig 83E), the visceral part covering the alimentary tract, the lungs, and the heart. The connecting portions are variously designated as mesenteries, mesocardia, ligaments, and omenta, but all of them have the same essential structure, namely, two layers of serous membrane united back to back and developed by approximation of separate coelomic cavities (Fig 109A).

The early coelom is a continuous cavity from end to end, but before long it becomes subdivided in the following manner into pericardial, pleural, and peritoneal cavities.

C THE SUBDIVISIONS OF THE EMBRYONIC BODY CAVITY

It is not easy to describe the way in which the embryonic coelom becomes subdivided into the adult compartments, because of the complicated spatial relations involved. In the following paragraphs is given merely an outline of the main features of the process, illustrated chiefly by diagrammatic figures. Many details are purposely omitted.

The process may be summarized thus. First, the anterior end of the body cavity, containing the developing heart, becomes separated by the formation of a partition which walls it off from the pleuro-peritoneal part. A little later the two pleural sacs, enclosing the growing lungs, become separated from the peritoneal cavity by the completion of the diaphragm.

The Separation of the Pericardium

In the early development of the body cavity the anterior end (the pericardial cavity) is much in advance of the more posterior portions. In embryos of 2-3 mm. (four weeks) the pericardial cavity has already become of good size and is partly shut off from the posterior part of the body cavity by the septum transversum, a thick mass of mesen-

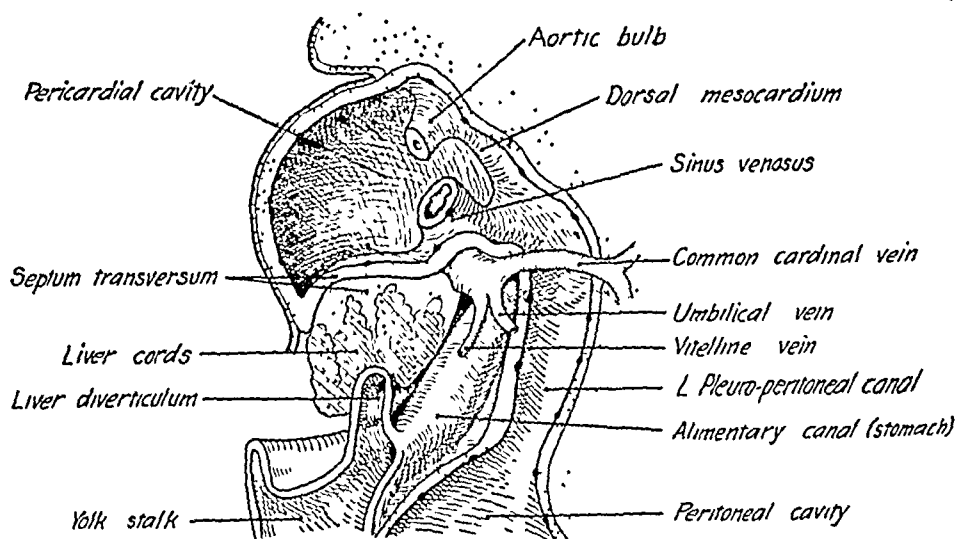


FIG. 103. Drawing from model of human embryo 3 mm. long (about 4 weeks). Section a little to left of median plane. The heart is omitted. (After His in Kollmann's *Handatlas*.)

chyme through which the vitelline veins enter the heart (Figs. 101B, 102, and 103). The septum transversum separates the pericardial region from the pleuro-peritoneal part except for two narrow canals designated as the dorsal parietal recesses, or more properly as pleuro-peritoneal canals (Figs. 101, 102, and 103). These canals are bounded ventrally by the septum transversum, laterally and dorsally by the body walls, and medially by the esophageal part of the gut and its thick mesodermal supports (the dorsal and ventral mesenteries) (Fig. 102).

In embryos as small as 4 mm. the lung buds are already beginning to push out from the sides of the thick ventral mesentery of the esophagus, bulging into the two pleuro-peritoneal canals (Fig. 105A). The mesothelium covering the expanding lung buds forms the visceral pleura (Figs. 99 and 105).

The complete separation of the pericardial cavity from the pleuro-peritoneal cavity is accomplished by the growth of a partition, the pleuro-pericardial membrane, across the cephalic end of each canal,

just cephalad to the growing lungs. These membranes form at the level of the common cardinal veins (Figs 103 and 104), and in fact are outgrowths from the ridges on the lateral body walls, in which

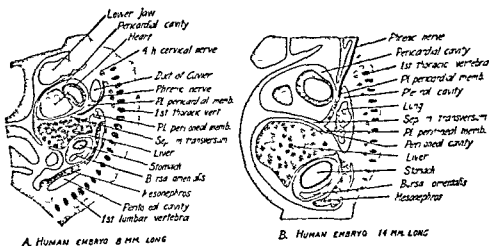


FIG 104 Sections through two human embryos a little to the left of the mid-sagittal plane. They show pleuro-pericardial and pleuro-peritoneal membranes, the septum transversum, and associated structures. (After Mall.)

these veins lie. The separation is completed in embryos of about 11 mm.

The Separation of the Pleural and Peritoneal Cavities

With the closure of the cephalic ends of the pleuro-peritoneal canals as described above, the canals become converted into two blind extensions or recesses from the anterior end of the peritoneal cavity (Fig 107A). Each recess then becomes separated by the growth of a pleuro-peritoneal membrane across it, just caudad to the lungs. Thus are formed the pleural cavities. The pleuro-peritoneal membranes grow out from the septum transversum and complete the closure by fusion with the body wall in embryos of about 19 mm (Figs 104 and 107).

The pleural cavities are at first small, but as the lungs grow the pleuro-peritoneal membranes shift caudad, causing rapid elongation of the pleural cavities (Fig 107). At the same time great lateral expansion of the pleural cavities into the body wall takes place by encroachment upon its loose mesenchyme. This results not only in lateral growth but also in very marked dorsal and ventral expansion, so that the pleural cavities soon occupy space on either side of the vertebrae and the pericardial cavity (Fig 105). Thus the pericardial cavity comes to lie between the ventral parts of the pleural cavities.

The pericardial membrane, by the same process, comes to include an extensive new area in addition to the earlier pleuro-pericardial membrane (Fig. 105).

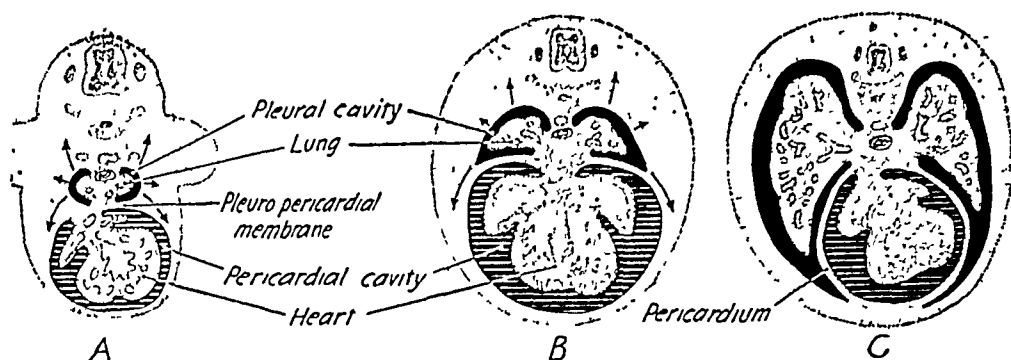


FIG. 105. Cross-sections to show expansion of pleural cavities into body wall and the formation of the pericardial membrane. Somewhat diagrammatic. Arrows show directions of major growth. Embryos of about 9 mm., 15 mm., and 35 mm. (Adapted from Arey and others.)

The Development of the Diaphragm

With the formation of the pleuro-peritoneal membranes, the separation of the peritoneal cavity from the pleural and pericardial cavities becomes complete. The diaphragm has been formed in the process. The diaphragm is composed in the main of two portions: the ventral and primary part derived from the septum transversum, and two large dorso-lateral areas from the two pleuro-peritoneal membranes. It should be noted, however, that not the full thickness of the septum transversum participates in the formation of the diaphragm, but only its cephalic part. The developing liver occupies its caudal part, which becomes transformed into the supporting tissues and ligaments of the liver, as described later. The diaphragm also includes two narrow areas at its lateral margins formed from part of the body wall while the pleural sacs are expanding into it. There is also a small median, dorsal portion derived from the dorsal mesentery. The musculature of the diaphragm develops from two premuscle masses probably derived from the fourth cervical myotomes, which grow into the diaphragm while the septum transversum is still in the cervical region. This fact explains why the phrenic nerves supplying the diaphragm have their origins from the third and fourth cervical nerves (Fig. 104).

The Recession of the Diaphragm and Other Organs

During the development of the diaphragm some very important changes in the relative positions between organs take place.

are commonly known as migrations or recessions, because by these changes in position, certain organs which have their origin at cephalic or cervical levels attain their adult positions much farther caudad. These recessions are brought about by differential growth, some organs or regions growing more rapidly than others. Conspicuous among these migrating organs are the heart, the lungs, and the diaphragm.

The early heart lies at the level of the pharynx in the cephalic region. The pericardial cavity is a part of the coelom lying at the same level as the heart. The heart and pericardium always lie cephalad to the septum transversum (Fig 103). The pleural cavities when first formed are minute and, like the heart, lie cephalad to the septum transversum, which at that time is in the cervical region (Fig 104B). The rapid growth of the lungs and pleural sacs is doubtless an

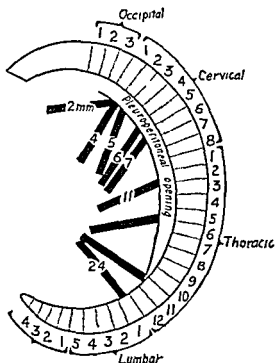


FIG 106 Diagram to show migration of the diaphragm during the growth of the embryo from 2 mm to 24 mm (After Mall)

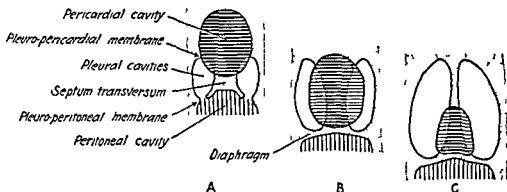


FIG 107 Diagrams to show differential growth of pleural and pericardial cavities and the migration of the pericardial cavity during the development of adult relations. Frontal projections

important factor in the recession of these organs. When first formed, the pleural sacs are much smaller than the heart, but when fully

grown, they exceed it severalfold in size (Figs. 104, 105, and 107). While the lungs are making their rapid expansion, the septum transversum and the developing diaphragm are carried caudad. The diaphragm reaches the level of the last thoracic segment by the seventh week (Fig. 106). The heart and pericardium follow the diaphragm down. This migration, coupled with the dorso-ventral expansion of the pleural sacs, brings about the final condition in which the heart lies between the inferior ends of the pleural sacs, whereas at the beginning it lay cephalad to them (Figs. 105 and 107).

The Development of the Mediastinum

When the adult relations of the thoracic organs have been attained, between the two pleural sacs there lie the heart and the pericardial cavity, the trachea, and the esophagus, as well as several large blood vessels, lymphatics, and nerve trunks, together with the intervening

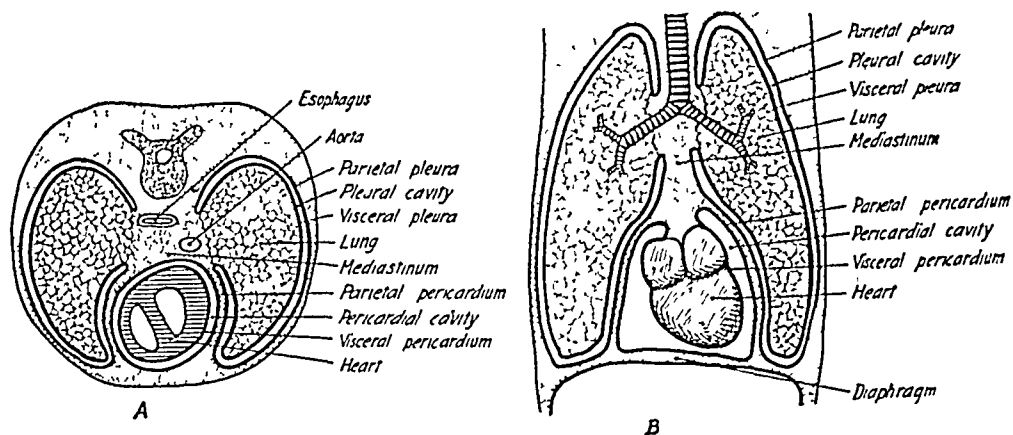


FIG. 108. Section through fully formed thorax showing in diagrammatic manner the relations of the pleural and pericardial membranes. *A*, cross-section. *B*, frontal section.

connective tissue. This whole region between the pleural cavities is the **mediastinum** (Fig. 108). It is developed essentially from the persisting mesenteries of the esophageal region of the gut, inasmuch as the two lateral cœloms (pleuro-peritoneal canals) remain separate during their development into the pleural cavities. Perhaps the only feature requiring special explanation is the presence in the mediastinum of the pericardium, a portion of the cœlom. As already pointed out, however, the pericardial cavity is a part of the cœlom which has migrated into the thorax from a higher level and has become largely enveloped by the pleural sacs on account of their great ventral expansion. The pericardial cavity bears the same relation to the mesodermal heart

as do the other serous cavities to the entodermal gut. Both the heart and the pericardium are associated with the ventral mesentery of the esophageal gut.

D THE PERITONEAL CAVITY AND THE PERITONEUM

Under this heading is described the development of the abdominal peritoneum. Description of the parts of the peritoneum that are in relation to the urogenital organs is deferred until Chapter XVII.

The peritoneal part of the coelom is, almost from its first formation, in communication with the exocoelom around the yolk stalk (Figs 101 and 102). With the complete closure of the body wall, however, this communication is obliterated (Figs 83 and 84, pp 125 and 126). The formation of the gut wall and the dorsal and ventral mesenteries has already been described in Chapter XI. There remains now to be considered the behavior of the primitive mesenteries in the development of the more complicated and puzzling adult conditions.

In the regions below the diaphragm the dorsal mesentery persists from end to end, but it becomes greatly modified by differential

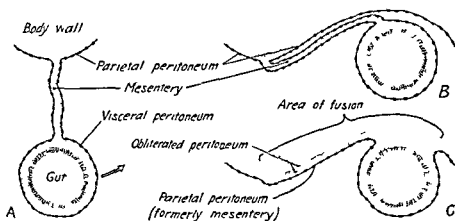


FIG 109 Diagrams showing mode of obliteration of mesenteries and the fixation of the gut to the body wall by fusion of areas of peritoneum. A, primitive condition; B and C show mode of fixation, for example, of ascending or descending colon.

growth and fusion. Serous membranes frequently fuse during development when two mesothelial surfaces come into contact. In such fusions the mesothelium disappears, leaving a connective tissue union which shows no evidence of the original separation (Fig 109). The ventral mesentery is a very transient structure, except the part between the diaphragm and the umbilicus (the region of the stomach and duodenum). This part is formed in a special manner because of its relations to the septum transversum and the liver.

The Ventral Mesentery and Its Derivatives

The liver bud, as it develops from the ventral side of the duodenal portion of the entodermal gut, grows into the mesenchyme of the septum transversum, which at this time lies opposite the duodenum (Fig. 103). The septum transversum, however, cannot long contain the growing liver, which soon expands caudad into the abdominal portion of the *cœlom* (Fig. 104). Before long there are thus produced two parts of the septum transversum: an anterior part adjacent to the pericardial cavity and a posterior part containing the liver (Figs. 103 and 104). The anterior part becomes a portion of the diaphragm, and the posterior part furnishes the connective tissue of the liver and the ventral mesentery of the stomach and duodenum. As the liver continues to grow, the right and left portions of the *cœlomic* cavity invade the septum transversum cephalad and laterad to the liver, largely separating the diaphragmatic portion from the part containing the liver (Figs. 104*B*, 111, and 112). The areas where the separation does not take place become the falciform ligament of the liver in the mid line and the coronary and triangular ligaments to either side (Figs. 111, 113*D*, and 114). During fetal life the umbilical vein runs in the caudal margin of the falciform ligament from the umbilicus to the liver. After birth this vein degenerates to form a solid cord of fibrous tissue, the round ligament of the liver (Fig. 113).

During the early growth of the liver the right and left *cœlomic* cavities invade also the region of the septum transversum between the liver and gut, but there remain in the mid plane of the body the hepato-gastric and hepato-duodenal ligaments, which connect the ventral side of the gut to the dorsal side of the liver. These ligaments constitute the lesser omentum (Figs. 111 and 112).

The lesser omentum when first formed lies in the mid-sagittal plane, but with the change of form and position of the stomach it comes to lie in a frontal plane and connects the liver to the lesser curvature (original ventral side) of the stomach (Figs. 110, 111, and 112).

The Dorsal Mesentery and Its Derivatives

The dorsal mesentery is, in its early development, a plane sheet of serous membrane supporting the simple gut. Its parietal attachment is along the mid-dorsal *cœlomic* wall (Fig. 113*A*). With the great increase in length of the gut and the resultant foldings, the originally simple mesentery becomes correspondingly complex. Its main divisions are described in the following paragraphs.

The Mesentery of the Small Intestine

The great elongation of the small intestine necessitates a corresponding growth of the intestinal margin of the mesentery, whereas its parietal margin, attached to the coelomic wall, elongates but little. Consequently there develop the elaborate folds of the mesentery proper, which radiate out from a relatively short root (the *radix mesenterii*) on the dorsal coelomic wall. This attachment shifts some-

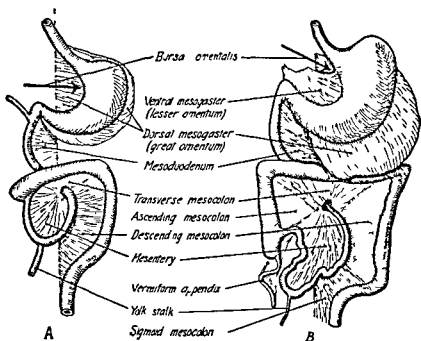


FIG 110 Figures showing in somewhat diagrammatic manner the intermediate history of the mesenteries as seen from a ventral view *A*, at 7 or 8 weeks. The ventral mesogastrium is omitted. The arrow points into the bursa omentalis *B*, a later stage, showing the growth of the mesogastrium and fusion of mesocolon to body wall. (Redrawn from Kollmann's *Handatlas*.)

what from the mid line toward the right, so that its adult position is oblique, extending from the duodeno-jejunal flexure to the ileo-cæcal junction (Fig 114). The only striking local departure from this mode of development is in the duodenal region, where the torsion of the intestinal loop brings the duodenum against the dorsal wall of the coelom behind the transverse mesocolon, where it fuses and loses its mesentery (Figs 110, 113*B*, and 114). The pancreas lies in this part of the mesentery, and consequently it also becomes fused to the abdominal wall (Figs 111*F* and 112).

The Mesentery of the Large Intestine

In the developing mesentery of the large intestine three chief regions soon are recognizable: the ascending, transverse, and descending mesocolons, corresponding to the three divisions of the colon (Fig. 110A). During further development of the colon its ascending and descending portions and their mesenteries come into contact with the dorsal abdominal wall, to which they fuse, thus obliterating these mesenteries and making these parts of the colon closely adherent to

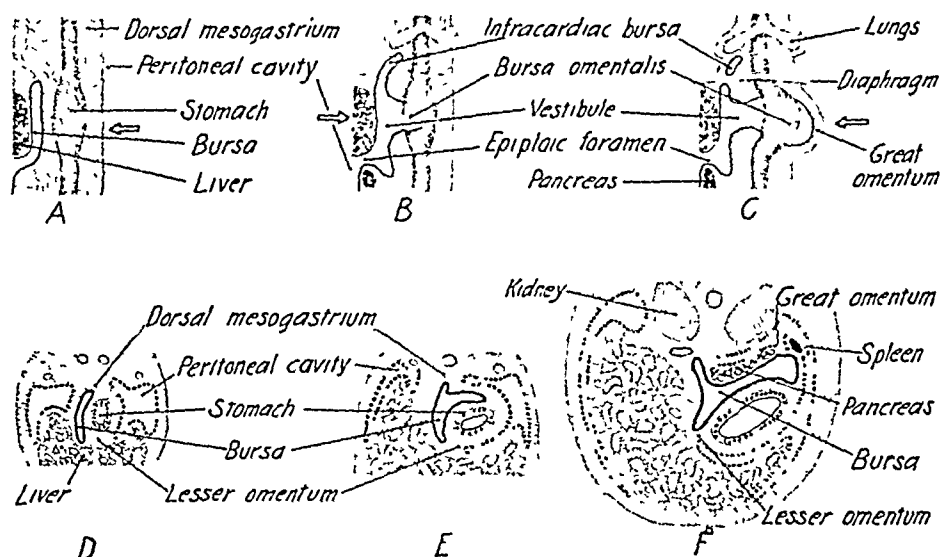


FIG. 111. Early development of lesser peritoneal sac. A, B, and C, showing invagination of lesser sac into the thick mesogastrium, as in human embryos 3 mm, 4 mm., and 17 mm. in length. Shown diagrammatically as transparencies from ventral aspect. D, E, and F, cross-sections through corresponding embryos at levels indicated by arrows in A, B, and C. Differential shading for greater and lesser sacs. (Adapted from Broman)

the body wall (Figs. 109, 110B, and 114). The transverse colon does not form such fusion but retains its suspension by the transverse mesocolon. The parietal attachment, however, because of certain fusions, shifts from the primitive longitudinal position to a transverse direction (Figs. 113B and 114). The transverse mesocolon is further modified by fusion with the dorsal mesogastrium, as is described in the following paragraphs. The sigmoid mesocolon persists.

The Mesentery of the Stomach (Dorsal Mesogastrium)

The dorsal mesogastrium becomes greatly modified in the formation of the great omentum and the bursa omentalis (lesser peritoneal sac), so that its primitive, diagrammatic relations become obscured.

The bursa omentalis has its beginning in embryos of 3 mm while the dorsal mesogastrium is still a thick, primitive structure (Fig 111A and D) The bursa omentalis appears first as an invagination of a part of the coelom into the right side of this mesentery, the invagination progressing toward the left and dorsad to the stomach (Fig 111) The opening of this sac into the general peritoneal cavity is the epiploic foramen The sac expands progressively toward the left, and its wall (the dorsal mesogastrium) develops into a large sac, the great omentum, with its parietal attachment to the mid-dorsal body wall and its visceral attachment to the dorsal side of the stomach

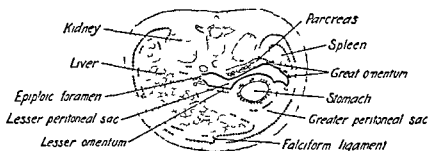


FIG 112 Cross-section showing greater and lesser peritoneal sacs when fully developed, as in adult Follows Fig 111F

(Fig 111F) When the stomach assumes its adult shape and position the great omentum is consequently attached to the greater curvature, and its large sac hangs down over the intestines (Figs 110, 112, and 113)

The cavity of the lesser peritoneal sac then lies dorsad to the stomach and extends caudad between the two limbs of the great omentum, it communicates with the general peritoneal cavity by means of the epiploic foramen (Figs 112, 113, and 114) The epiploic foramen is bounded ventrally by the free (originally caudal) margin of the lesser omentum, dorsally by the inferior vena cava, cranially by the caudate lobe of the liver, and caudally by the duodenum (Figs 112 and 114)

Several fusions of serous membranes contribute to the further development of the great omentum The part behind the stomach fuses to the dorsal body wall, so that its adult attachment bears obliquely toward the left (gastro-splenic ligament in Fig 114) The pancreas lies largely in the dorsal mesogastrium and so becomes fused to the body wall (Figs 111, 112, and 113) Another portion of the descending limb of the great omentum fuses to the transverse mesocolon and colon, so that the transverse mesocolon becomes a combined

structure, one of its surfaces being a part of the mesogastrium (Fig. 113D). The two sides of the saccular part below the transverse colon also usually fuse and obliterate this part of the cavity (Fig. 113C and D). The part of the omentum hanging from the transverse colon in front of the coils of the small intestine is the great omentum

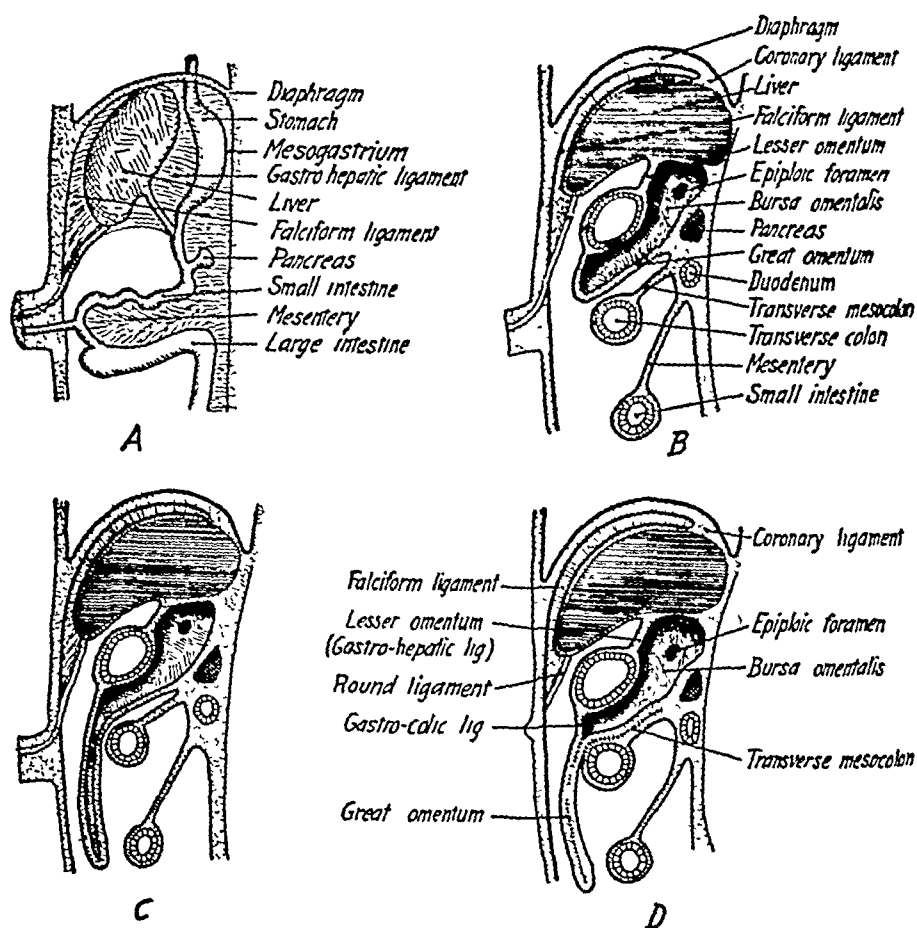


FIG. 113. Diagrams to show the development of the great omentum and associated structures. A, lateral dissection of embryo (6 weeks). B, sagittal section of embryo (about 8 weeks). C, sagittal section of fetus (about 4 months). D, sagittal section through adult. (Modified from Kollmann.)

of adult anatomy (Fig. 113D). The remaining part between the stomach and the colon is the gastro-colic ligament. After the completion of these changes, the lesser peritoneal cavity is limited as shown in Figs. 112, 113D, and 114.

It is worthy of note that, in the early development of the lesser peritoneal sac, a slender branch grows cephalad between the esophagus and the right lung, but the formation of the diaphragm

cuts it off. In some adults it persists as an isolated serous cavity, the infracardiac bursa (Fig 111*B* and *C*)

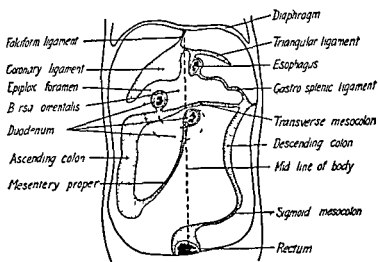


FIG 114 Ventral view showing reflections of peritoneum from adult body wall. Primitive embryonic reflection was from mid-dorsal line (Adapted from Morris' *Anatomy*)

E ANOMALIES

The most striking anomalies involving the body cavities are those in which the ventral wall of the body is incomplete because of failure of the right and left halves of the somatopleure to unite, so that an opening is left through which the viscera protrude. The defect may extend from neck to pelvis or may be more restricted, may involve all the layers of the body wall or only some of them. Congenital defects of a less extreme nature, known as hernia, are common, the most frequent being in the inguinal and umbilical regions. The most common diaphragmatic hernia, allowing the abdominal viscera to protrude into the pleural cavities, is due to incomplete development of the pleuro-peritoneal membranes and is more frequent on the left side. Failure of development of the pleuro-pericardial membrane allows permanent communication between pleural and pericardial cavities.

Minor variations of the mesenteries and omenta are due chiefly to non-fusion in certain regions, for example, persistence of ascending and descending mesocolons and non-fusion of the two sheets of the great omentum.

CHAPTER XIV

THE HEART AND BLOOD VESSELS

Human circulation is established early, about the middle of the fourth week, at a time when other systems of organs are just beginning to take form. At first this circulation is a very simple system, carrying blood between the chorion and yolk sac and the embryo. As the embryo grows and becomes more complicated, the circulation within it becomes more extensive. At birth the extra-embryonic parts are discarded.

A. THE EARLY DEVELOPMENT OF HUMAN CIRCULATORY ORGANS

The Formation of the Earliest Blood Vessels. The earliest blood vessels develop from groups of cells known as angioblasts (vessel formers). These primordia appear first in the chorionic mesoderm, as early, according to some authorities, as the eleventh day. Very soon they are seen also in the body stalk and the mesoderm of the yolk sac. These vessel-forming primordia are at first solid but begin to attain lumens about the seventeenth day. At first they are separate endothelial sacs, but they gradually unite to form a capillary network in which larger vessels soon form by coalescence of capillaries (Fig. 116).

The first vessels in the embryo appear a little later than in the extra-embryonic membranes, about the time of the formation of the first somites (twenty-one days) (Fig. 117*B*). These early vessels in the embryo probably form *in situ* by transformation of mesenchyme cells into endothelium, though some authorities believe they grow into the embryo from extra-embryonic regions. The blood vessels quickly become organized into a complete system. Circulation of blood begins about the twenty-fifth day. From this small and simple system of vascular channels the continued extension of the growing system takes place by sprouting of the endothelium to produce extension of the capillary system as the embryo grows.

Origin of the Layers of the Blood Vessels. The earliest blood vessels consist of endothelium only. The embryonic vessels remain of this primitive nature for considerable time, a condition which makes

the modification of vascular channels during development an easy matter In the capillaries and sinusoids of the adult this primitive simplicity of structure persists In the arteries and veins, however, other layers of muscular and fibrous tissue are added in varying amounts, these layers being derived from the surrounding mesenchyme

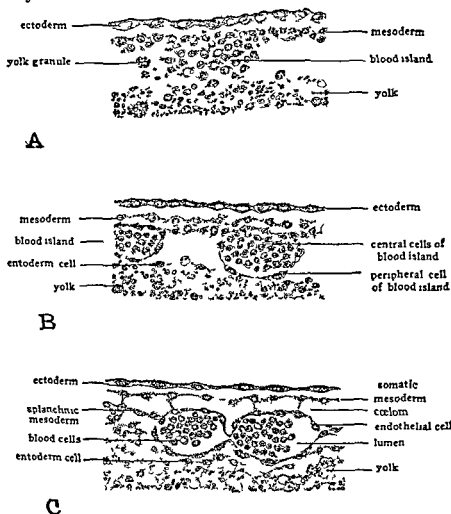


FIG 115 Three stages in the differentiation of blood islands into blood vessels containing blood, as seen in chick embryos A 18 hours, B, 24 hours, C, 33 hours (Patten in *Early Embryology of the Chick*, P Blakiston's Son & Co, Philadelphia)

The Formation of the Earliest Blood The earliest blood is produced in the yolk sac About the middle of the second week numerous knots of rounded cells known as blood islands form in the mesoderm of the yolk sac (Fig 115) During the latter part of the week the superficial cells of the islands become flattened and so form an

endothelial covering, enclosing the inner cells. The enclosed cells are the primitive blood cells, which are described more fully in Chapter XVI. These cells soon float in the plasma, which is being formed at the same time. The endothelium of adjacent islands coalesces to form

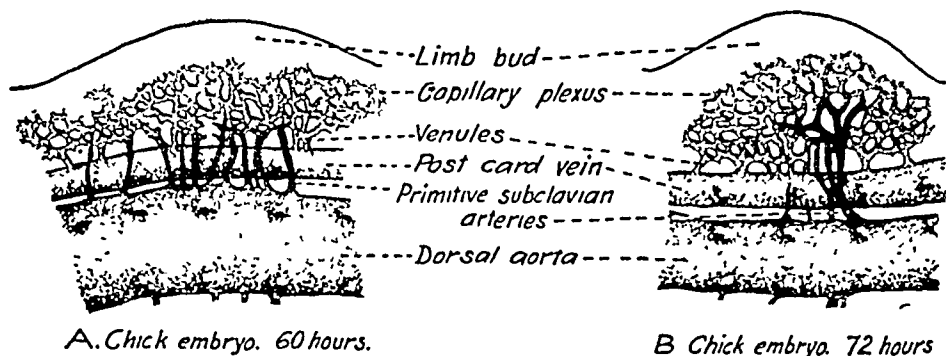


FIG. 116. Figures showing the capillary plexus which precedes the formation of definite blood vessels. Anterior limb bud of chick embryos, showing primitive subclavian artery. (Redrawn from Evans in *Am. Jour. Anat.*)

a capillary network which joins the empty capillaries of the chorion and body stalk. Thus the earliest blood cells are produced within the vessels themselves, and both the blood cells and the endothelium form from the mesoderm of the yolk sac.

The Early Development of the Heart. Most of the early development of the heart takes place immediately below the pharyngeal part of the entodermal gut tube (Fig. 117). The very earliest primordia of the heart and the pericardial part of the coelom, however, seen about the twentieth day, lie not within or below the head fold, but a short distance in front of it, whence they are carried to their position below the pharynx by the folding process which forms the head and fore gut. Figure 101A, p. 147, shows the place of origin of the pericardium and heart, and Figs. 101B, p. 147, and 117 show the position of the heart after it has reached the pharyngeal region.

The early heart differs from the earliest blood vessels in that, from the very beginning, in addition to the endothelial layer, it has also an outer, thicker layer, the epi-myocardium (Figs. 117 and 118). The epi-myocardium is a specialized part of the splanchnic mesoderm in the floor of the early pericardial cavities. The endothelium of the heart tube forms by the union of numerous separate units which lie between the epi-myocardium and the entoderm of the pharynx (Figs. 117 and 118). These uniting endothelial units very soon form two tubes (right and left) nearly separate from each other, which at one end are continuous with the blood vessels of the yolk sac and at the other end with the vessels of the embryo.

Before long the two endothelial tubes coalesce completely into a single median tube (Fig 118) The right and left epi-myocardial parts likewise unite to form a single tube As they are coming together, there persists for a time the dorsal mesocardium, suspending the heart

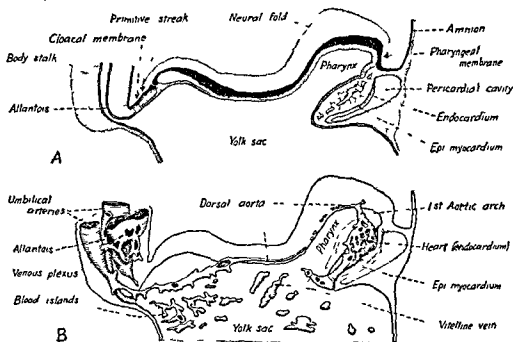


FIG 117 Early blood vascular system Human embryo with two somites (about 21 days), showing heart and blood vessels in the embryo and adjacent regions of yolk sac and body stalk. The separate endothelial foci have partly united to form vessels, this process is farther advanced in the body stalk than elsewhere. A sagittal section B, reconstruction showing heart and vessels of the right side, other structures only in outline (Adapted from Ingals in *Cont to Emb*, Carnegie Inst.)

from the pharynx (Fig 118) The union of the two lateral parts does not form a ventral mesocardium Before long the dorsal mesocardium disappears also, so that the heart is suspended from the pericardial wall only at either end by the connecting vessels

B THE CIRCULATION OF THE EMBRYONIC PERIOD

The embryonic phase of circulation may be said to begin with the earliest vascular primordia late in the third week, even though the actual circulation of blood does not begin until nearly a week later The general plan of embryonic circulation, which is entirely different from that of the adult, is shown diagrammatically as it would appear in ventral view in Fig 119 and in side view in Fig 120 The following are the characteristic features

The Heart. In the earliest stages the heart is essentially an enlarged vessel having well-developed power of contraction and lying ventral to the pharynx. Very early four divisions may be recognized in it: **sinus venosus**, **atrium**, **ventricle**, and **bulbus cordis**, which will be more fully described in a later paragraph (Fig. 131A).

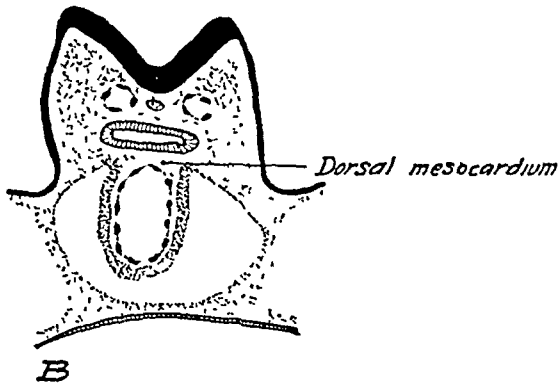
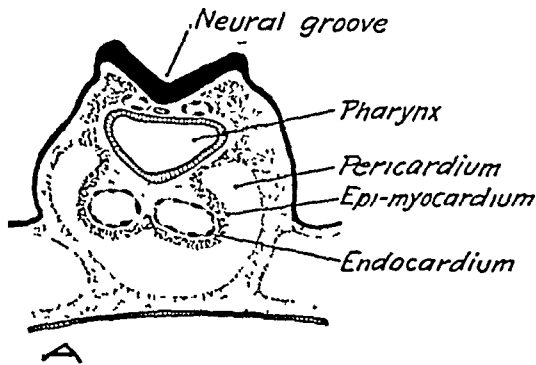


FIG. 118. Diagrams to show the formation of the primitive heart tube in the human embryo by the fusion of two vessels. Shows also the origin of the muscular wall of the heart from a portion of the coelom, and the endocardium from the endothelium of primitive blood vessels. A, embryo 1.8 mm. long B, embryo 2 mm. long (Diagram A based upon Keibel and Elze; B, upon Mall)

embryo and give off numerous small branches to the body of the embryo, not shown in Figs. 119 and 120. They also give off two pairs of larger vessels, the **vitelline arteries** to the yolk sac and the **umbilical arteries** to the chorion frondosum

2. *The ventral aorta* is the vessel through which blood leaves the heart at the cephalic end. After a very short course it expands into an enlargement known as the **aortic sac**, from which arise the **aortic arches**.

3 *The aortic arches* are vessels which develop in the arches of the pharyngeal wall between the branchial grooves. They connect between the ventral and dorsal aortas. There are six pairs of these vessels, but

to the pharynx. Very early four divisions may be recognized in it: **sinus venosus**, **atrium**, **ventricle**, and **bulbus cordis**, which will be more fully described in a later paragraph (Fig. 131A).

The Arteries. The embryonic arteries are the **dorsal aortas** and their branches, the **ventral aorta**, and the **aortic arches**.

1. *The dorsal aortas* are a pair of vessels running the length of the embryo just dorsal to the developing gut. At first they are separate through their whole length (Fig. 119), but soon they fuse in the posterior region, making a Y-shaped vessel double in the region of the pharynx but single in all the region posterior to the pharynx. Figure 120 shows an early stage in the union of the two dorsal aortas. The dorsal aortas are the main distributing vessels of the

not all of them are present at any one time, those at the anterior end developing first and degenerating before the most caudal ones have formed. It should be noted that in man the fifth arch is of variable occurrence, at best being a very small vessel and in other embryos not being evident at all.

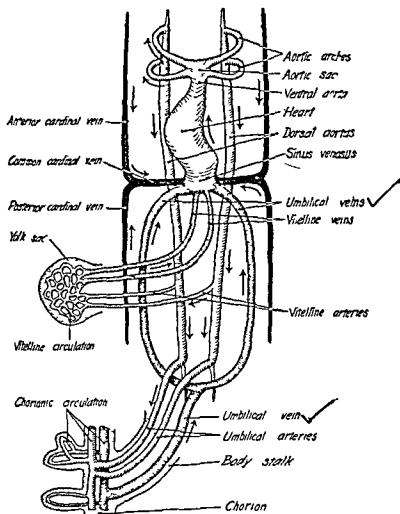


FIG 119 Diagrammatic ventral view of human circulation of the embryonic period. Arrows show the direction of blood flow.

The Veins The embryonic veins are the anterior cardinal veins, posterior cardinal veins, common cardinal veins, vitelline veins, and umbilical veins.

1 The anterior cardinal veins are a pair of vessels collecting blood from the anterior region of the embryo (Figs 119 and 120).

2 The posterior cardinal veins are a corresponding pair returning blood from the posterior part of the body. There are many small

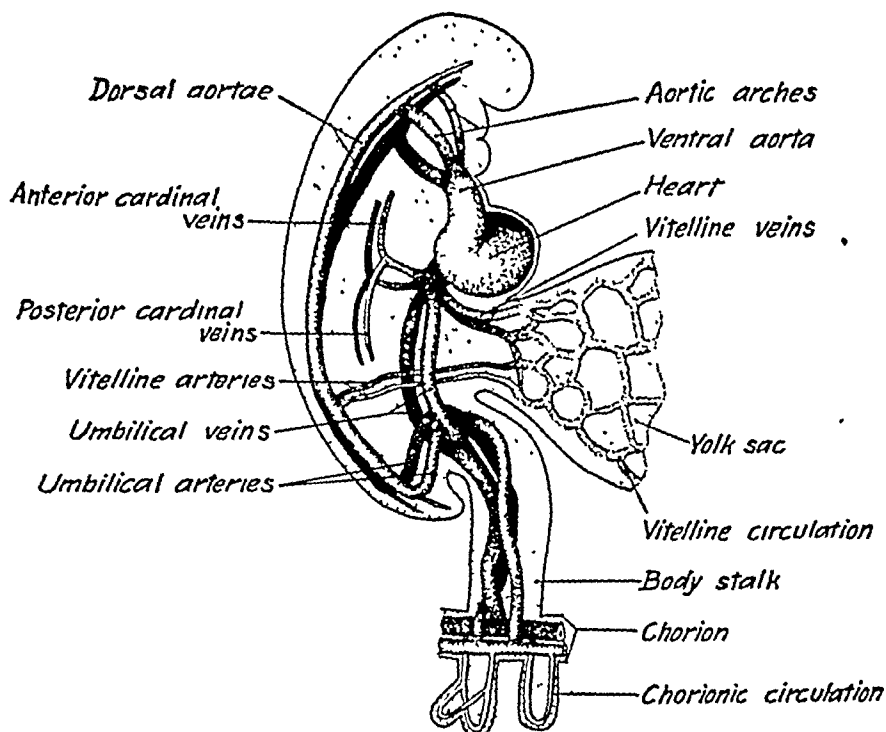


FIG. 120. Diagrammatic lateral view of human circulation of the embryonic period. Shows vessels about as in embryo 2.6 mm. long (Fig. 23). The two dorsal aortas have begun to fuse.

veins tributary to the anterior and posterior cardinal veins which collect blood from both the body wall and the internal organs.

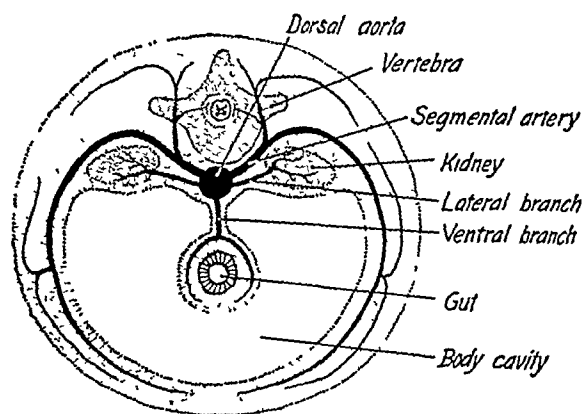


FIG. 121. Diagrammatic cross-section through embryo, showing the three sets of branches of the dorsal aorta.

3. The common cardinal veins (ducts of Cuvier) are a pair of short vessels, one on each side, formed by the union of the anterior and posterior cardinal veins. They discharge into the sinus venosus of the heart.

4. The vitelline veins are a pair of vessels carrying blood from the yolk sac into the sinus venosus.

5. The umbilical veins return blood from the chorion to the sinus venosus.

In the body stalk there is one umbilical vein, but as it enters the body of the embryo it divides into the right and left vessels.

From the foregoing description it will be recognized that the circulation of the embryonic period is on a wholly different plan from that of the adult human being. In the first place it has a large extra-embryonic portion (vitelline and umbilical vessels) necessary for the nutrition of the embryo. The importance of the umbilical vessels has already been emphasized in Chapter VI on the placenta. In the second place, the intra-embryonic vessels in their general plan resemble those of fishes rather than those of the adult human being. This feature cannot be said to bear any special relation to the peculiar needs of intra-uterine life, but seems rather to be reminiscent of ancestral conditions retained by the embryo but lost by the adult.

C TRANSFORMATION FROM EMBRYONIC TO FETAL CIRCULATION

Toward the close of the second month the embryonic type of circulation gradually becomes transformed into the fetal type, which is, in all its main features, like that of the adult, though it still retains the large extra-embryonic portions and has a few other peculiarities made necessary by the conditions of intra-uterine life. In the following pages will be described the development of only the larger arteries and veins of the trunk region, no attempt being made to trace the history of the smaller vessels or the circulation of the limbs.

a The Development of the Arteries

The Descending Aorta and Its Branches The part of the dorsal aorta caudad of the pharyngeal region persists with little change as the descending aorta of the adult. The adult vessels arising as branches from it develop as follows:

Beginning approximately at the caudal end of the pharynx there are numerous branches from the dorsal aorta, arranged in three series as shown in Fig. 121.

1 *The Dorsal Segmental Arteries* These arteries supply the body wall of the embryo, including the neural tube (Fig. 121). There are probably twenty-nine pairs, exclusive of two very transient pairs in the occipital region. They run between the somites and are accordingly often called intersegmental arteries. The first cervical pair arises from the dorsal aorta at about the level of the fourth aortic arch vessel (Fig. 122). The vessels of the seventh cervical pair supply the capillary plexus of the arm buds and become the subclavian arteries. The fifth lumbar pair become the common iliac arteries of the leg buds. The majority of the others develop rather directly into the intercostal and lumbar arteries.

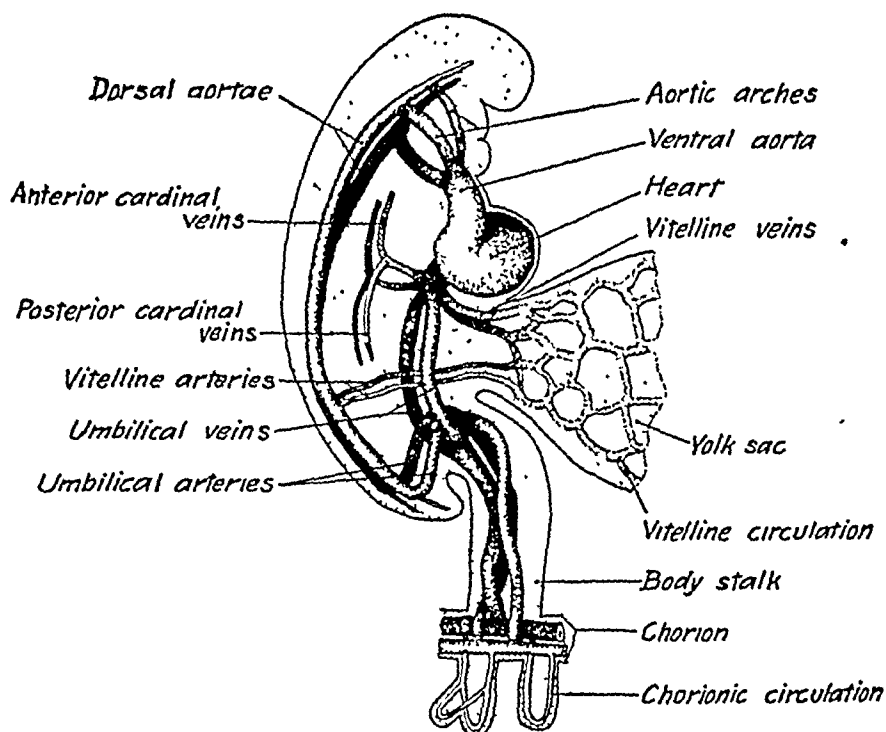


FIG. 120. Diagrammatic lateral view of human circulation of the embryonic period. Shows vessels about as in embryo 2.6 mm long (Fig. 23). The two dorsal aortas have begun to fuse.

veins tributary to the anterior and posterior cardinal veins which collect blood from both the body wall and the internal organs.

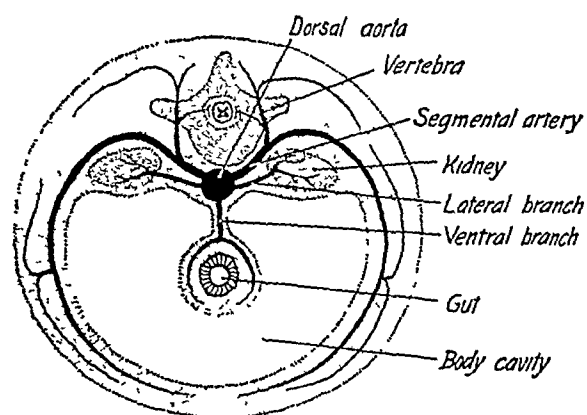


FIG. 121. Diagrammatic cross-section through embryo, showing the three sets of branches of the dorsal aorta.

3. The common cardinal veins (ducts of Cuvier) are a pair of short vessels, one on each side, formed by the union of the anterior and posterior cardinal veins. They discharge into the sinus venosus of the heart.

4. The vitelline veins are a pair of vessels carrying blood from the yolk sac into the sinus venosus.

5. The umbilical veins return blood from the chorion to the sinus venosus.

In the body stalk there is one umbilical vein, but as it enters the body of the embryo it divides into the right and left vessels.

In embryos of about 9 mm. a series of anastomoses form between the cervical segmental arteries. These soon develop into paired longitudinal vessels, the vertebral arteries, which lose all connection with the aorta except through the subclavian arteries (Figs. 122 and 123). By these two channels the brain receives blood in addition to that coming through the carotids. The internal mammary and inferior

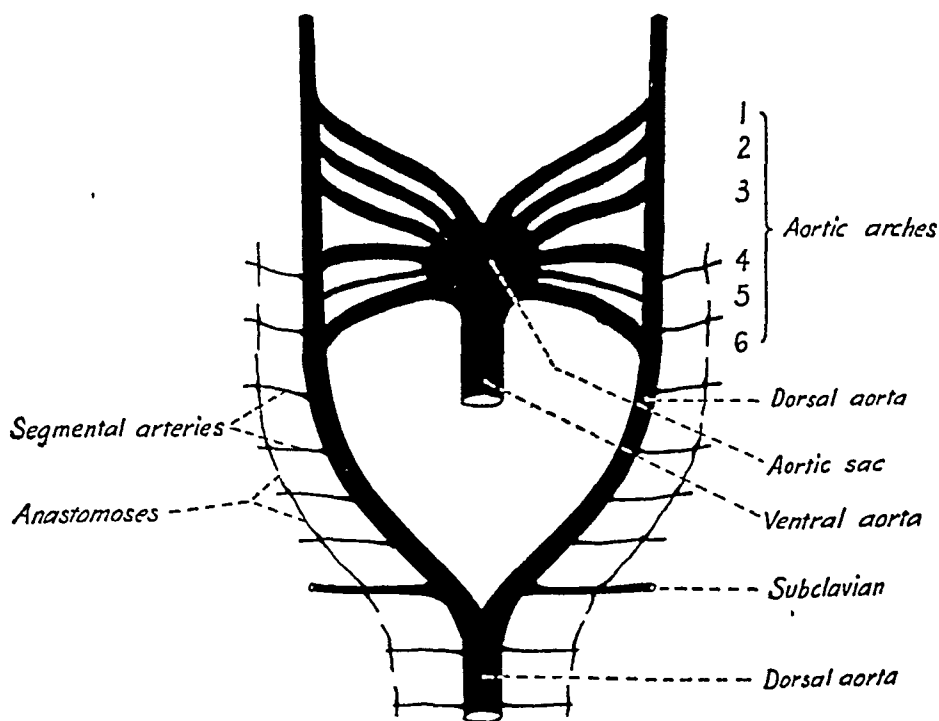


FIG. 122. Diagram showing the arteries of the pharynx and adjacent region as in the embryonic period. Drawn as if all arches were present at the same time, and all spread out in one plane. (Mainly after Congdon.)

epigastric arteries are formed by similar anastomoses in the thoracic and abdominal regions, but they retain the several original connections to the aorta (the intercostals and the lumbar).

2. *The Lateral Branches.* The lateral branches arise from the dorsal aorta somewhat ventrad to the dorsal series (Fig. 121). They supply certain of the mesodermal viscera—the mesonephros, the metanephros, the sex glands, and the suprarenal glands. From them develop the adult suprarenal, inferior phrenic, internal spermatic (or ovarian), and renal arteries.

3. *The Ventral Branches.* These branches belong to the splanchnic mesoderm of the alimentary canal and the yolk sac. They are the vitelline arteries. At first they are paired and rather numerous, but the number becomes reduced and most pairs fuse to form single

The innominate artery is a persisting part of the aortic sac on the right side, which elongates to become a vessel. It corresponds to a short segment of the arch of the aorta on the left side (Figs 122 and 123).

The right and left common carotid arteries are the ventral ends of the third arch vessels. The external carotid arteries are branches running cephalad from the middle of the third arch vessels. The internal carotid arteries are continuations of the third arches beyond the

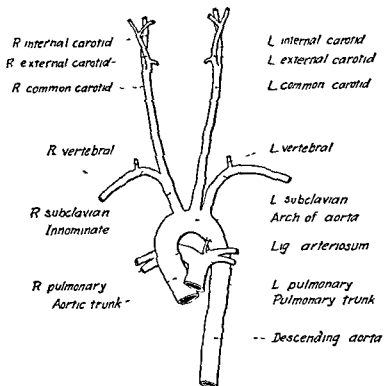


FIG 125 Outline drawing to show the adult form of the arteries which develop from the aortic arches, the ventral aorta, and the anterior ends of the dorsal aortas. The same vessels are present as shown in Fig 123, the difference in appearance being due chiefly to the migration of the heart into the pharynx, which causes a change in the direction of certain of the vessels.

origins of the external carotids, together with the anterior ends of the dorsal aortas, which in the embryo very early extend into the head about the neural tube as the primitive carotids.

Right and left subclavian arteries develop from the seventh cervical segmental arteries, which distribute to the developing arms. The left subclavian includes only that vessel itself, the right one, however, has in addition a portion of the right dorsal aorta and the right fourth arch vessel. This peculiar asymmetrical condition is due to degener-

The following embryonic vessels degenerate: the entire first, second, and fifth aortic arches, and the dorsal part of the sixth, also the parts of the dorsal aortas between the third and fourth arches, and the part of the right aorta between the subclavian and the fork. This last degeneration is responsible for the arch of the adult aorta being on the left side only. In amphibia and reptiles both sides persist, in birds only the right side, in all mammals only the left. From the parts which do not degenerate, permanent vessels develop as follows.

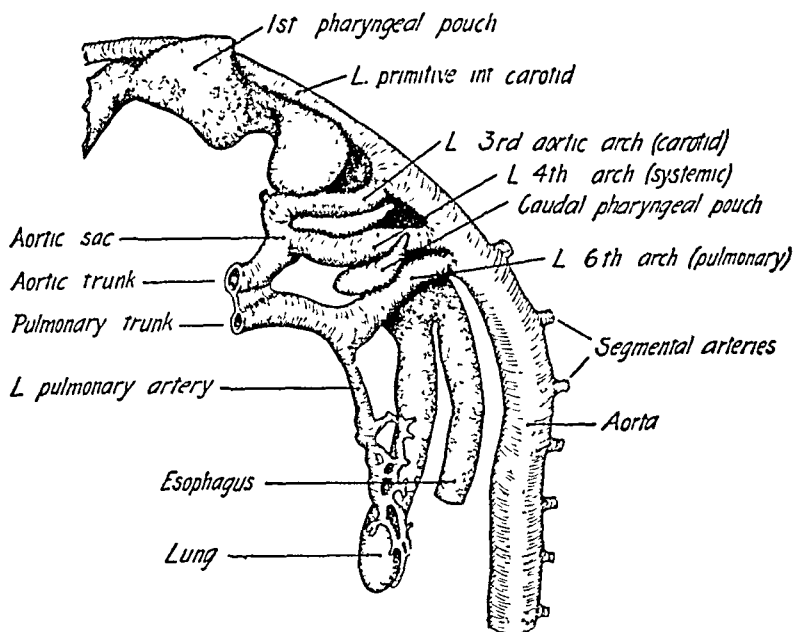


FIG. 124. Side view of the pharynx and aortic arches of a human embryo 11 mm. long (6 weeks) to show the actual form of the vessels at an intermediate stage of the transformation and the relation of these vessels to the pharynx.

(Redrawn from Congdon, in *Cont. to Emb.*, Carnegie Inst., Washington.)

The ventral aorta splits longitudinally into two vessels, the **aortic trunk** and the **pulmonary trunk**. At the same time the aortic sac also divides in such a manner that the pulmonary trunk connects to the vessels of the sixth arch, and the aortic trunk to the third and fourth arches (Figs. 122 and 123). The relation of these two trunks to the heart will be described in a later section.

The **arch of the aorta** is formed from the following embryonic divisions: (1) the aortic trunk (part of the ventral aorta); (2) part of the aortic sac on the left side; (3) the left, fourth aortic arch; and (4) part of the left dorsal aorta caudad to the fourth arch.

The arteries which in the adult come off from the arch of the aorta develop thus.

The parts of the vitelline veins between the liver and the heart are the primitive hepatic veins. From the parts distad to the liver the portal vein develops, formed from persisting parts of both of the

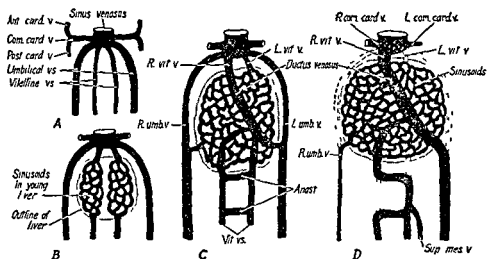


FIG 126 Diagrams showing the early development of the portal system of veins

vitelline veins and three anastomosing veins between them (Figs 126 and 127). When the digestive tract forms, the mesenteric veins from its wall (branches of the vitelline veins) are tributaries of the portal vein.

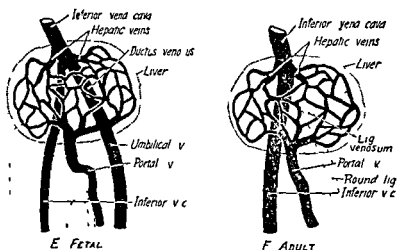


FIG 127 Diagrams showing the fetal and adult stages of the portal system of veins. The network of vessels in the liver is drawn less close than in the preceding figure, merely to simplify the drawing.

Though the portal system develops primarily from the vitelline veins, the umbilical veins also become involved, for as the developing liver continues to grow, its lateral expansion brings its sinusoids into

ation of the segment of the right dorsal aorta just above the fork. For this reason the basal portion of the right subclavian corresponds developmentally to a portion of the arch of the aorta.

The right and left pulmonary arteries develop from two segments: (1) a new vessel growing from the middle of the sixth arch vessel to the developing lung and (2) the ventral end of the sixth arch vessel (Figs. 123 and 124). These vessels receive their blood from the pulmonary trunk, which develops, as described on page 172, by a spiral, longitudinal splitting of the ventral aorta. The dorsal end of the right sixth arch vessel promptly degenerates, but the corresponding part of the left arch persists until just after birth as the ductus arteriosus, through which blood from the pulmonary trunk flows into the arch of the aorta. Figure 124 shows the vessels of the pharyngeal region in a human embryo 11 mm. long (six weeks).

It should be remembered that, while the changes just described are taking place, the heart is migrating from the neck into the thorax. This migration of the heart causes a change in the direction of the vessels connecting with it. The effects are seen by comparing Figs. 123 and 125, which show that the embryonic vessels shift their positions until the innominate, left common carotid, and left subclavian come to arise from the top of the arch, whence they extend toward the head instead of to the sides, as they do in the earlier stages. The transformation of the arch vessels is practically completed by the close of the seventh week, except that the migration of the heart has not yet produced its full effect.

b. The Development of the Veins

The Portal Circulation. The portal circulation, including the portal veins, the hepatic veins, and the sinusoids of the liver, develops from the vitelline veins. Starting with the primitive embryonic condition shown in Figs. 119 and 126A, the general course of development is this: When the liver bud grows out from the gut, it makes contact with the two vitelline veins not far from their entrance into the heart. As the growing liver breaks up into the cords of liver cells, the vitelline veins adjacent to the cords break up into corresponding sinusoids, which thus from their inception are intimately interwoven with the liver cords. An early stage in this process is shown in Fig. 126B. Soon the sinusoids from the two veins unite into one system (Fig. 126C). Before long the left vitelline vein between the liver and the heart degenerates, so that all the blood from the liver must enter the heart through the base of the right vein (Fig. 126D).

The parts of the vitelline veins between the liver and the heart are the primitive hepatic veins. From the parts distad to the liver the portal vein develops, formed from persisting parts of both of the

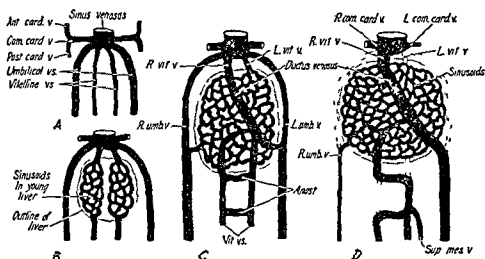


FIG 126 Diagrams showing the early development of the portal system of veins

vitelline veins and three anastomosing veins between them (Figs 126 and 127). When the digestive tract forms, the mesenteric veins from its wall (branches of the vitelline veins) are tributaries of the portal vein.

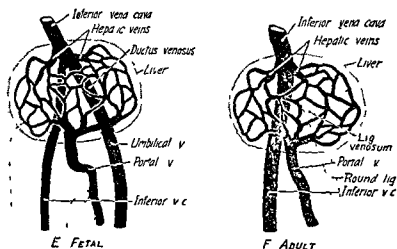


FIG 127 Diagrams showing the fetal and adult stages of the portal system of veins. The network of vessels in the liver is drawn less close than in the preceding figure, merely to simplify the drawing.

Though the portal system develops primarily from the vitelline veins, the umbilical veins also become involved, for as the developing liver continues to grow, its lateral expansion brings its sinusoids into

contact with the two umbilical veins, with which they form anastomoses (Fig. 126C). Then the parts of the umbilical veins between the anastomoses and the heart degenerate, so that the umbilical blood can reach the heart only through the liver (Fig. 126D). About the same time the entire right umbilical vein degenerates. The persisting left vein shifts to the mid line, where it runs in the caudal margin of the falciform ligament as the umbilical vein of fetal life (Fig. 113, p. 160).

At the same time, by coalescence of sinusoids, a good-sized channel develops through the liver, the ductus venosus, which carries the greater part of the blood from the umbilical vein (part of it goes through the liver sinusoids). The hepatic veins develop as larger channels through which the sinusoids drain into the ductus venosus (Fig. 127). The adult relations of the hepatic veins are attained when the part of the ductus venosus to which they are tributary becomes part of the inferior vena cava (Figs. 127 and 134).

Shortly after birth, the part of the umbilical vein within the body degenerates to become the round ligament of the liver, (Figs. 113, p. 160, and 127). At the same time the ductus venosus degenerates to become the ligamentum venosum.

The Superior Vena Cava. In the development of the veins cephalad of the heart, the paired anterior cardinal veins and common cardinal veins (Fig. 119) give place in the following manner to the unpaired superior vena cava and its branches.

The first step in the development of the superior vena cava is the formation of a new, oblique cross-connection, the left innominate vein, between the two anterior cardinal veins. This connecting vein increases in importance, and the part of the left anterior cardinal vein between it and the left common cardinal vein degenerates, so that all the blood from the left side finally crosses over and enters the heart through the proximal part of the right anterior cardinal and right common cardinal veins (Figs. 128 and 129). Thus the superior vena cava becomes established from two veins: (1) the right common cardinal vein and (2) the basal part of the right anterior cardinal vein (Figs. 128 and 129).

The part of the right anterior cardinal vein above the entrance of the left innominate becomes the right innominate vein. The extensions of the two cardinal veins into the head become the internal jugular veins, whereas the external jugulars arise somewhat later as new branches. The subclavian veins develop from a pair of the segmental veins which drain into the cardinal veins. They at first open into the posterior cardinal veins, but during the migration of the heart into

the thorax their connections shift to the anterior cardinals, where they attain their adult relation with the innominate and external jugular veins. The migration of the heart into the thorax also changes to some extent the direction of the large veins connecting to it and converts the picture shown in Fig 129 into one like the adult.

The left common cardinal vein, together with the left horn of the sinus venosus, becomes the coronary sinus (Fig 129).

The Inferior Vena Cava The development of the inferior vena cava is an extremely complicated process involving a shifting maze of vessels, many of which are of very short duration. The process is of interest because it explains certain peculiarities of the adult inferior vena cava and tributary vessels, as well as the frequent variations to which these vessels are subject. Only the main features of the process will be presented here.

In the development of the inferior vena cava, three pairs of temporary veins are involved. (1) The posterior cardinal veins, which are the earliest veins returning blood from the posterior end of the embryonic body, run along the dorsal sides of the mesonephroi (embryonic kidneys), from which they receive numerous tributaries (Fig 119). These veins also receive the segmental veins which return blood from the body wall and which in the adult become the intercostal and lumbar veins. (2) The subcardinal veins, which appear a little later than the posterior cardinals, run along the ventral sides of the mesonephroi. These veins make numerous anastomoses with the posterior cardinal veins through the mesonephroi. (3) The supracardinal veins appear at a still later time and run along the dorso-median sides of the mesonephroi. Figure 128 shows a very diagrammatic plan of these veins, drawn as if spread out in one plane.

There are frequent anastomosing vessels, a very few of which are shown in Fig 128) between these three pairs of vessels. The largest anastomosis, known as the renal anastomosis, is at the level of the developing kidneys (Fig 128). It should also be observed that the primitive renal veins connect to the part of the renal anastomosis between the subcardinal and supracardinal veins, and that the primitive adrenal and genital veins connect to the subcardinal veins (Fig 128).

The adult conditions are brought about by degeneration of appropriate parts of this complicated system of embryonic vessels, the main features of which are shown in Figs 128 and 129.

From these figures it will be seen that the inferior vena cava is composed of the following segments. (1) Part of the ductus venosus, which, it will be remembered, enters the heart through the base of the

right vitelline vein (Figs. 126 and 127). The inferior vena cava, accordingly, enters the heart through the proximal end of the right vitelline vein. (2) A new vein which connects the ductus venosus with the right subcardinal vein. These two parts comprise the hepatic portion of the vein. (3) The right subcardinal vein as far as the renal

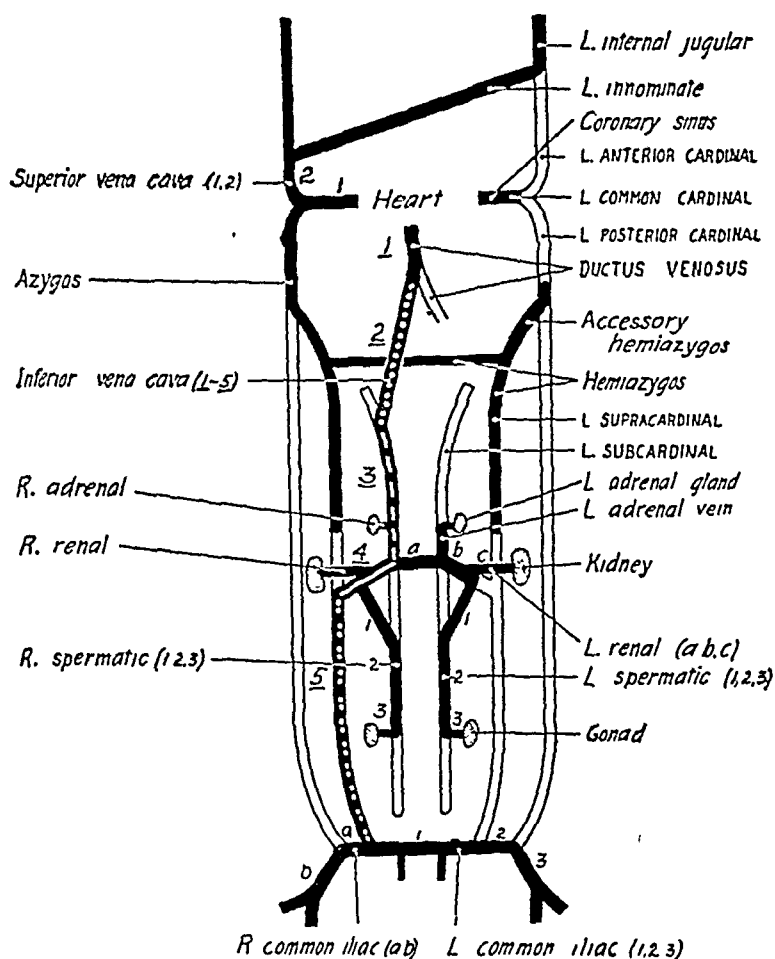


FIG. 128. Diagram to show the development of the superior and inferior venae cavae and certain other veins. The general plan is that of the embryonic veins, drawn as if spread out in one plane. Persistent veins are shown in black; degenerating vessels are left unshaded. The five segments of the inferior vena cava are designated by numbers and differential shadings. (Based upon description by McClure and Butler.)

anastomosis. (4) The right renal anastomosis between subcardinal and supracardinal veins. (5) The right supracardinal vein from the renal anastomosis to the iliac anastomosis. These five segments, indicated by numbers and different shadings in Fig. 128, straighten out as shown in Fig. 129 to form the adult inferior vena cava. The

development of the inferior vena cava is about completed by the close of the eighth week

A study of Figs 128 and 129 will show how it comes about that the adult left renal vein is longer than the right and why the supra-renal and spermatic veins on the left side empty into the renal vein

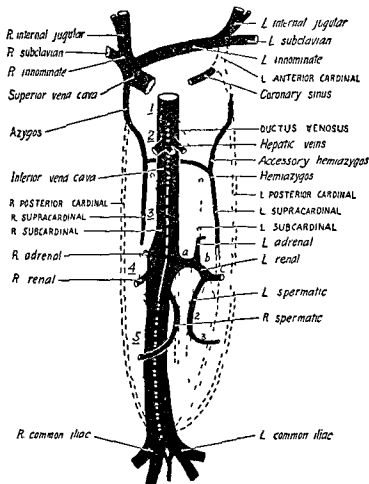


FIG 129 The development of the superior and inferior venae cavae and certain other veins Shows same facts as Fig 128 but this figure is based more upon the adult relations, with degenerated embryonic vessels shown in broken lines (Modified from McClure and Butler in *Am Jour Anat*)

and on the right side into the inferior vena cava It is also apparent why the inferior vena cava lies a little to the right of the mid line (and of the aorta) and why the common iliac veins are not quite symmetrical

The origin of the veins of the azygos group is also shown in Figs 128 and 129 The azygos vein is formed from portions of the right posterior cardinal and supracardinal veins, and the hemiazygos from

part of the left supracardinal and an anastomosis to the azygos; the accessory hemiazygos is the adult representative of part of the left posterior cardinal which enters the azygos through the left supracardinal and an anastomosis. /

It will be quite evident from the preceding account how great are the possibilities for the production of variations in adult veins by the persistence of portions of embryonic veins which commonly degenerate and the degeneration of parts which usually persist. For example, a double inferior vena cava from the level of the kidneys is sometimes formed by the persistence of both right and left supracardinals instead of only the right. The inferior vena cava sometimes follows the left instead of the right supracardinal, resulting in a partially reversed relation of certain tributary vessels (renal, adrenal, and spermatic veins). Many other variations also occasionally occur, all of which may be explained in a similar manner.

The Pulmonary Veins. The pulmonary veins develop in the mesenchyme surrounding the entodermal lung buds. They grow toward the heart and connect with the left atrium.

c. The Development of the Heart

The Form of the Early Heart. As already observed in the description of the early circulatory system, the heart is an enlarged, pulsating vessel which receives blood through three pairs of vessels, the common cardinal, the umbilical, and the vitelline veins, which enter its posterior end. The blood after passing through the heart leaves it at the anterior end by a single artery, the ventral aorta (Fig. 119).

Almost from the first appearance of the heart tube the following divisions can be recognized in it: (1) the *sinus venosus*, a small part with thin walls into which the veins enter; (2) the *atrium*, a somewhat enlarged portion, also with thin walls; (3) the *ventricle*, a thick-walled portion; and (4) the *bulbus cordis*, a tapering part of the ventricle which connects with the ventral aorta (Fig. 130A). In the development of the adult heart from this primitive heart tube, three main processes are operative: (1) bending, (2) unequal growth, and (3) division into right and left sides.

Bending and Unequal Growth of the Heart Tube. The heart tube grows in length faster than the pericardial cavity and as a result becomes bent abruptly in two places, taking somewhat the form of the letter N, to accommodate it to the short space in which it lies (Fig. 130A). After the bending, the sinus venosus and the atrium lie

in the original position in the mid line, the ventricular part is bent abruptly ventrad, caudad, and to the right, and the bulbus cordis again extends cephalad to the ventral aorta. Further change brings the atrium to a position cephalad of the ventricle, with the sinus venosus on its dorsal surface. This produces relations something like those of the adult, with the apex of the ventricle directed caudad and the atrium lying cephalad, the opposite to the condition in the early embryo (Fig 130B)

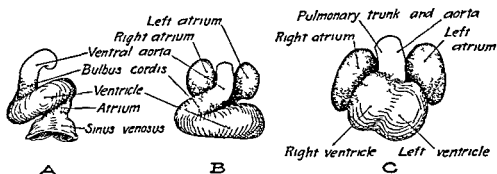


FIG 130 The development of the external form of the heart as seen in ventral view. Distinctive shadings are used to make the parts more apparent (The forms of the hearts are based upon figures by His). *A*, embryo 2.15 mm long. The heart tube is bent like letter *N*. *B*, embryo 4.3 mm long. The atrium has migrated to a position cephalad to the ventricle and dorsad to the ventral aorta and has expanded into right and left pouches. The sinus venosus is no longer visible, because it now lies on the dorsal side of the atrium. *C*, embryo 10 mm long (nearly 6 weeks). Division of ventricle into right and left sides is in progress and the bulbus cordis has been incorporated into the right side. The ventral aorta is also undergoing longitudinal division.

A still closer approach to the adult appearance is brought about by the expansion of the atrium into two good-sized pouches, the future right and left atria, one on either side of the bulbus cordis (Fig 130B). At the same time the ventricle increases greatly in size and its walls become muscular and very thick. An external groove indicates the division into right and left ventricles, with the bulbus cordis connecting to the right side (Fig 130C). The proximal part of the bulbus cordis later becomes incorporated mainly into the right ventricle, of which it forms the infundibulum, and its distal part, along with the ventral aorta, splits to form the pulmonary artery and the ascending aorta, as described on p 172. The sinus venosus does not persist as a separate chamber of the adult heart but soon becomes incorporated into the right atrium.

The Division of the Heart into Right and Left Sides In the division of the heart into right and left sides, essentially what happens

is that a longitudinal partition is formed from end to end, through both atrium and ventricle. Thus the right and left atria and the right and left ventricles are produced. Because this division takes place while the heart is bent in the fashion just described, the process is somewhat difficult to describe by either words or pictures. It is more easily understood if we assume it to take place while the heart is straight. Accordingly it is so shown in Figs. 131 and 132, which are

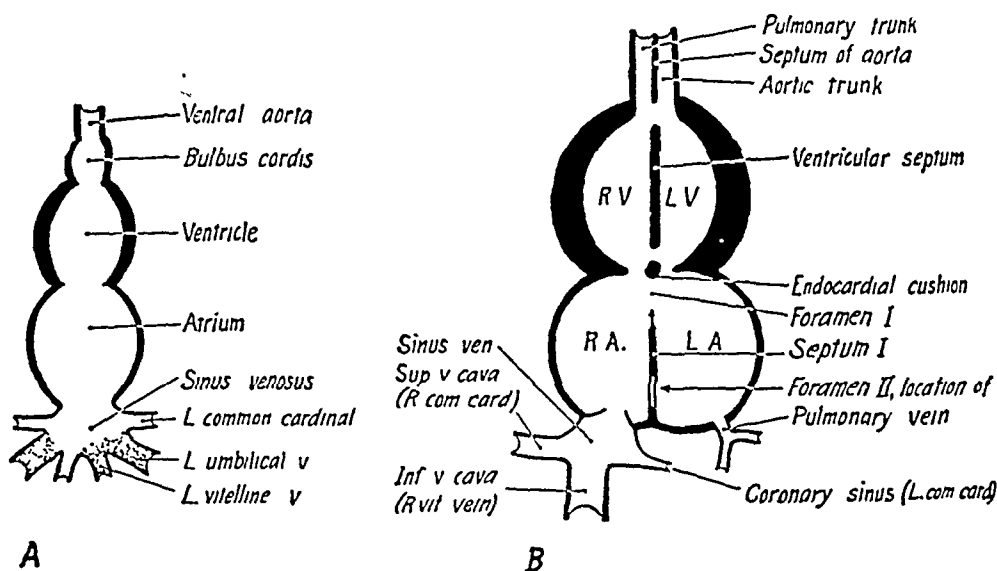


FIG 131. Diagrams showing the development of the four chambers of the heart. In these figures the embryonic heart is shown as if it were straight instead of bent. A, the early two-chambered condition. The three entering veins which are shaded are the ones which degenerate at about this time and are not shown in drawing B. B shows the beginnings of the septum, shifting of the sinus venosus to the right side, degeneration of certain veins, and the appearance of the new pulmonary veins.

not drawings of actual hearts, but rather diagrams of what would happen if the division took place while the heart tube was straight.

The Atrial Septum. The septum of the heart forms in several separate parts (Fig. 131B), which become connected end to end into one continuous wall. In the atrium two incomplete septa form, both to the left of the sinus venosus (Fig. 132). The **primary septum** (septum I) grows across the atrial cavity from its dorso-cephalic wall and fuses with the endocardial cushions at the atrio-ventricular canal. But it never becomes a complete septum, for before it closes the gap (foramen I) by union with the endocardial cushions, a new opening (foramen II) forms in it. The **secondary septum** (septum II) forms a little later than septum I and on its right side. It never becomes

complete, its opening being the foramen ovale. The openings in the two septa allow blood to flow through from the right atrium into the left, but not in the reverse direction, because septum I acts as a valve, the valve of the foramen ovale. During fetal life it is kept pushed toward the left by the flow of blood from the right atrium into the left (Figs 132 and 133). This subject is further discussed on p 186.

The Fate of the Sinus Venosus In connection with the formation of the septum of the heart, the behavior of the sinus venosus is of importance. In its primitive condition the sinus venosus is connected symmetrically to the atrial part of the heart and receives three pairs of veins with symmetrical arrangement (Fig 131A). When the superior and inferior venae cavae are formed, however, all the blood from the placenta and most of that from the body of the embryo enters the sinus venosus through its right side, by way of the former right common cardinal and right vitelline veins, and only a small volume enters its left side through the small coronary vein, formerly the left common cardinal vein (Figs 126, 129, and 131A). The result is that the left side of the sinus venosus becomes much reduced in size, and the venous connections of the heart are shifted to the right side of the atrium.

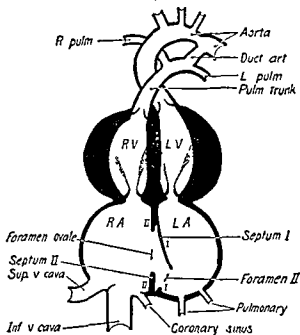


FIG 132 Diagram of the fetal heart, drawn as if the heart tube were straight. A continuation of the series in Fig 131. Shows completion of the septum, absorption of the sinus venosus into wall of right atrium, and division of ventral aorta into aortic and pulmonary trunks.

When the atrial septum is formed, it lies in such a position that the entire sinus venosus is on its right (Fig 131B). The pulmonary veins, which later connect to the left side, are new vessels, arising in connection with the developing lungs and making connection with the left side of the atrium (Fig 131).

The superior and inferior venae cavae at first enter the right atrium through a common passage, the sinus venosus. At the entrance of the

is that a longitudinal partition is formed from end to end, through both atrium and ventricle. Thus the right and left atria and the right and left ventricles are produced. Because this division takes place while the heart is bent in the fashion just described, the process is somewhat difficult to describe by either words or pictures. It is more easily understood if we assume it to take place while the heart is straight. Accordingly it is so shown in Figs. 131 and 132, which are

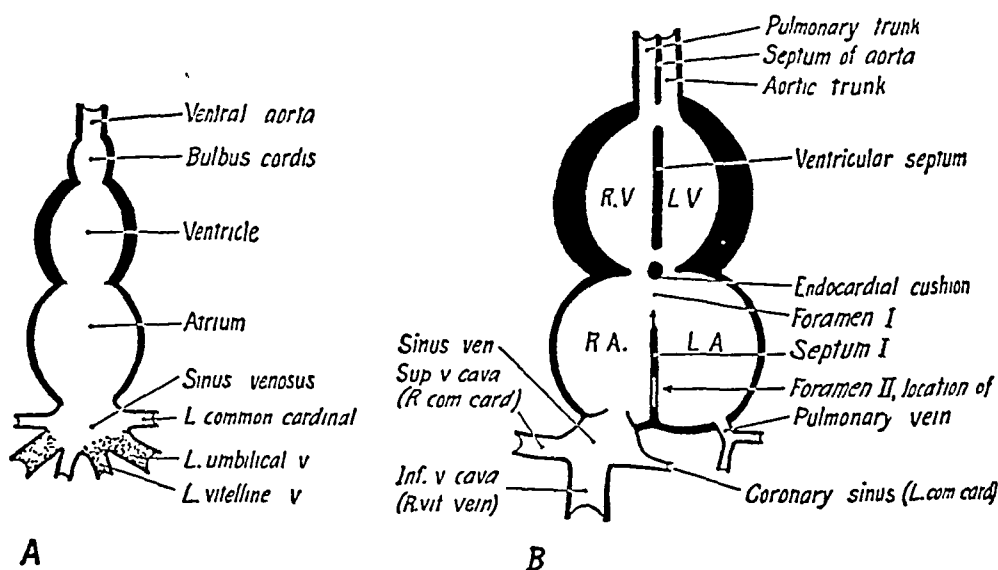


FIG. 131. Diagrams showing the development of the four chambers of the heart. In these figures the embryonic heart is shown as if it were straight instead of bent. *A*, the early two-chambered condition. The three entering veins which are shaded are the ones which degenerate at about this time and are not shown in drawing *B*. *B* shows the beginnings of the septum, shifting of the sinus venosus to the right side, degeneration of certain veins, and the appearance of the new pulmonary veins.

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The Ventricular Septum The ventricle becomes divided by a septum which grows out from the wall across the chamber and unites with the endocardial cushions and the septum of the aorta. When the ventricle divides, the bulbus cordis is not divided by the septum but, in the main, becomes a part of the right ventricle.

The Division of the Ventral Aorta The division of the ventral aorta to form the aortic and pulmonary trunks has already been described in the section on the arteries. This division is brought about by the formation of four longitudinal ridges in the endothelial lining of the vessel. Two of these, which are more prominent than the others, soon unite to form a longitudinal partition. This septum runs a spiral course, so that the pulmonary and aortic trunks which are separated by it twist about each other in such a way that the pulmonary trunk connects the right ventricle with the vessels of the sixth arch and the aortic trunk connects the left ventricle with the third and fourth arches (Figs 123 and 132). The semilunar valves of the aorta and the pulmonary artery are formed from the persistent proximal ends of the ridges which caused the division of the ventral aorta.

The Atrio-Ventricular Valves The atrio-ventricular valves arise as flaps on the walls of the openings, two on the left side, forming the bicuspid or mitral valve, and three on the right, giving rise to the tricuspid valve. These flaps at first include not only the endocardium but also part of the muscular wall. To their free edges are attached bundles of muscles, which are in reality portions of the heart wall which have not become consolidated into the general muscle mass. The muscular tissue of the valves soon degenerates, after which the valves are composed of fibrous tissue covered with endothelium. The muscle columns at the ends attached to the valves also degenerate to form the tendinous cords, whereas their other ends persist as the papillary muscles.

The Atrio-Ventricular Bundle The primitive muscular tissue in the developing heart is at first continuous from atrium to ventricle, but when the atrio-ventricular valves form, the muscle becomes interrupted by connective tissue at the atrio-ventricular canal, except for a slender strand in the septum. This strand develops into the peculiar kind of cardiac muscle known as Purkinje fibers, which make up the atrio-ventricular bundle (bundle of His) serving to coordinate the contractions of the two ends of the heart.

The primitive heart tube is first formed early in the fourth week, and all the main features of its development, as described in the preceding pages, are accomplished by the close of the eighth week.

sinus venosus into the atrium there are two flaps, the right and left valves of the sinus venosus (Fig. 131*B*). During the latter part of the second month the right atrium grows more rapidly than the sinus venosus, which causes the sinus venosus to flatten out so that it becomes part of the atrial wall and ceases to exist as a separate chamber. As a result the superior and inferior venae cavae come to open separately into the right atrium (Fig. 132).

The left side of the sinus venosus, together with the left common cardinal vein, at the same time becomes the coronary sinus (Figs. 131*B* and 132). The left valve of the sinus venosus fuses with the

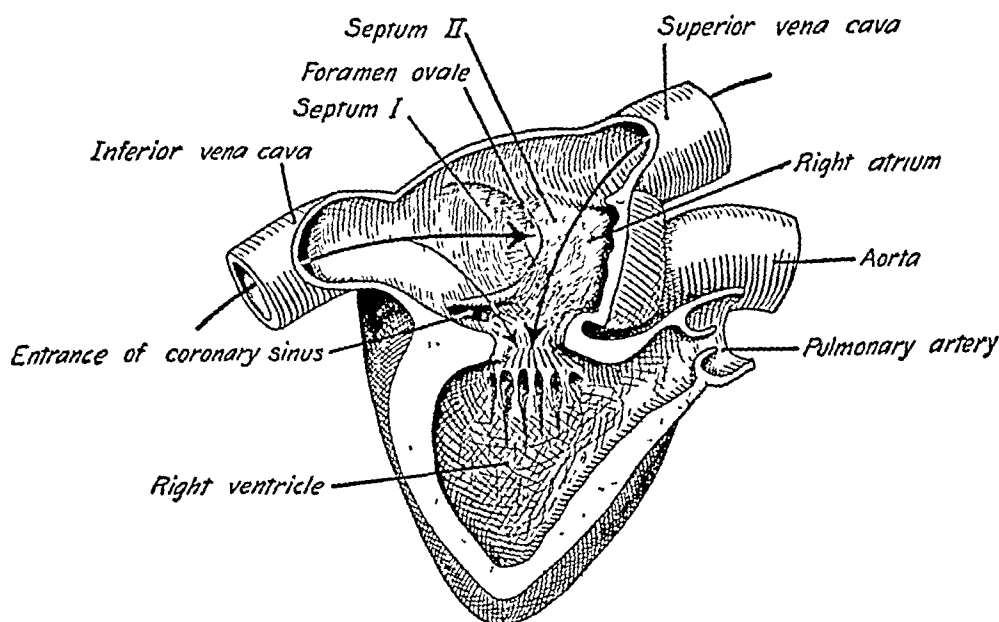


FIG. 133. Dissection of fetal heart from right side to show foramen ovale and the two septa. The arrows indicate the probable course of the two caval blood streams through the right atrium.

secondary septum; the right valve in part degenerates and in part persists to form the valve of the inferior vena cava and the valve of the coronary sinus.

The Division of the Atrio-Ventricular Opening. The opening between the atrial and ventricular parts of the early heart is a single narrow passage. The division of this passage into right and left sides begins with the formation of the two endocardial cushions, thickenings of the endocardial lining on the dorsal and ventral surfaces of the opening (Fig. 131). These unite with each other to form a bridge across the passage. This bridge unites with the atrial septum and with that of the ventricle.

handle only as much blood as the pulmonary circuit could carry away from it, and more would of necessity be forced through the foramen ovale. As it is, both ventricles of the fetal heart pump equal volumes of blood. Neither the foramen ovale nor the ductus arteriosus alone

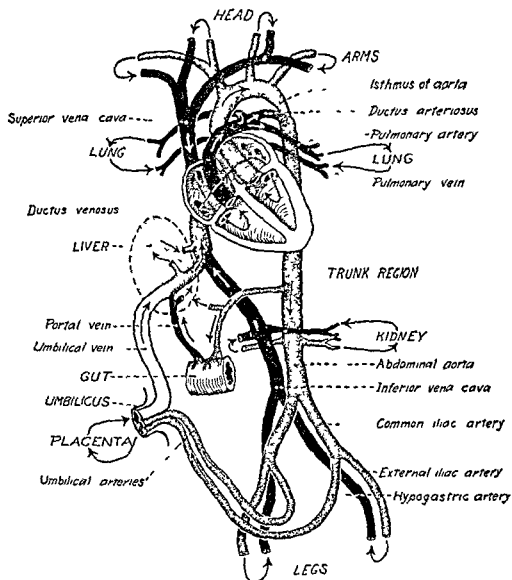


FIG 134 Fetal circulation. Varying impurity of blood suggested by intensity of shading

would serve to remedy the inequality between the two sides of the heart, and unequal development of the sides would result, inasmuch as structure and function in the developing heart are interdependent.

The Fetal Blood In the different vessels of the fetal circulation there are several grades of "purity" of blood, the exact quality in

D. TRANSFORMATION TO ADULT CIRCULATION

In the preceding pages were described the changes which transform the embryonic circulation into that of the fetal and adult periods. It may be well now to summarize and comment upon the characteristics of the circulation of each of these periods.

The Embryonic Circulation. The embryonic circulation is about the simplest possible type. It is designed merely to carry food materials from the placenta and distribute them to the embryo and to collect wastes from the embryo and carry them to the placenta, where the exchange of materials with the maternal blood takes place (Fig. 135A).

The Fetal Circulation. During the latter part of the embryonic period the circulation is thoroughly reconstructed, the embryonic type being changed into the adult type, except for a few features which characterize it as fetal (Fig. 134).

Although the digestive organs, the kidneys, and the lungs become well developed before the close of fetal life, throughout the fetal months, absorption, excretion, and respiration are carried on through the placenta. Accordingly the umbilical arteries and veins are large and important vessels.

Other important features of the fetal circulation result from the condition that the lungs are tardy in their development and the respiratory capillaries of the fetal lungs have much less capacity than those of the body generally. This inequality is further increased by the placental circulation, which is anatomically a part of the systemic circulation through the umbilical vessels (Figs. 134 and 135). The volume of blood returning to the left side of the heart through the pulmonary veins is accordingly very much less than that returning to the right side through the two caval veins.

The Fetal Heart. The fetal heart is enabled to take care of this peculiar situation by a delay in the complete separation of its right and left sides. Two special features contribute to this end. (1) The foramen ovale allows part of the large volume of blood entering the right atrium to flow directly into the left atrium and thus through the left ventricle into the systemic circuit. If it were not for this device the left side of the fetal heart would receive only the small volume of blood which returns from the developing lungs (Figs. 134 and 135). (2) The ductus arteriosus allows part of the blood from the pulmonary trunk to flow into the aorta and thence into the general circulation, until such time after birth as the pulmonary circulation develops sufficient capacity to carry as much blood as the systemic circuit (Figs. 134 and 135). Without this device the right ventricle would

still difference of opinion, however, as to how promptly these openings close

According to a view which has been widely accepted for many years, there is functional closure within a few minutes after birth, the ductus arteriosus promptly becoming constricted by muscular action and the foramen ovale closing by valve-like approximation of septa I and II. This closure of the foramen ovale is believed to be brought about by changed pressures in the two atria as follows. As soon as the umbilical cord is ligated, shutting off the umbilical vessels, there is a decrease in the amount of blood entering the right atrium through the inferior vena cava. It is also believed that at the same time the distention of the lungs by the first inspirations of air causes sudden expansion of the respiratory capillaries, allowing a greatly increased flow of blood through the pulmonary vessels into the left atrium, an effect which is also aided by the closure of the ductus arteriosus. The change in relative pressures thus produced in the two atria closes the valve of the foramen ovale. After this early functional closure of the foramen ovale and the ductus arteriosus, a permanent anatomical closure is gradually brought about by tissue growth during the next several months.

On the other hand, some authorities believe that in human infants the functional closure of these openings is gradual. They maintain that in the late fetal weeks the pulmonary vessels are already carrying enough blood to sustain life (though less than in the systemic vessels) and that at birth there is no great and sudden increase, but rather a smooth, steady rise in the pulmonary flow during the first few weeks after birth. It is believed that during these early weeks the functional closure of the ductus arteriosus and the foramen ovale is gradual, and that, in fact, if circulation is to be maintained smoothly, it is necessary that these passages continue to allow flow of blood, though in decreasing amounts, until the capacity of the pulmonary circuit becomes equal to that of the systemic circuit.

In the adult heart an oval depression, the fossa ovalis, marks the former location of the foramen ovale. The ductus arteriosus leaves a remnant, the ligamentum arteriosum, connecting the left pulmonary artery to the arch of the aorta. The ductus venosus likewise degenerates to leave the ligamentum venosum of the liver, and the part of the umbilical vein between the liver and the umbilicus becomes the round ligament of the liver. The parts of the umbilical arteries within the body also largely degenerate, their adult remnants being the hypogastric and superior vesical arteries and the two lateral umbilical ligaments.

each vessel being determined by the capillary region from which it comes and the mixing of blood by confluence of various streams. Purest of all is that in the umbilical vein returning from the placenta. Before this stream reaches the heart, however, it is diluted by the venous blood in the inferior vena cava (Fig. 134).

There has long been difference of opinion as to the amount of mixing in the right atrium, a question of interest since the inferior vena cava carries blood of higher purity than does the superior vena cava. Some investigators have believed that there is complete mixing, but some recent studies, mostly upon living fetuses of sheep, seem to confirm the older view that the mixing is only slight. It now seems clear that the stream from the inferior vena cava is divided in the right atrium by the configuration of the walls and its greater portion directed through the foramen ovale into the left atrium without dilution, whereas its lesser portion flows into the right ventricle, together with the entire flow from the superior vena cava (Figs. 133 and 134). It has also been shown that, as a result of this course of blood in the atrium, the blood going to the head and arms through the arteries arising from the aortic arch is of higher purity than that going to the trunk and legs through the descending aorta and its branches (Fig. 134). It has not been shown, however, that this distribution of blood has any developmental significance, though, very appropriately, the blood directed to the placenta is of the less pure grade (Fig. 134).

Changes at Birth. The following important changes in circulation take place at birth or very soon thereafter. The tying of the umbilical cord stops the outflow of blood through the umbilical arteries and its return through the umbilical vein. Thus the placenta is eliminated as a means of securing food and getting rid of wastes, these duties being suddenly thrown upon the organs of the child, which heretofore have not functioned. The kidneys must very soon begin to eliminate wastes, and before a great while the digestive organs must begin to supply foods.

The greatest and the immediate need of the new-born infant, however, is oxygen, without which its life is promptly extinguished. This need is met by the beginning of the respiratory movements, which are stimulated by the scarcity of oxygen and the increase in carbon dioxide resulting from shutting off the placental supply of oxygen.

It has long been known that shortly after birth both the foramen ovale and the ductus arteriosus close, completing the arrangement by which all the blood upon return from the body capillaries must go to the lungs before again starting on the systemic circuit. There is

vascular channels, serious maldevelopment of the heart or much mixing of blood through the opening may result. The cyanotic infants known as "blue babies" are of this type.

The blood vessels are subject to frequent variations of many kinds, brought about by persistence of different combinations of channels in the transformation from embryonic to adult circulation. Many of these variations in no way interfere with the normal functioning of the body. Some of the more striking anomalies are the following:

The ventral aorta may fail to divide into the pulmonary and systemic trunks, or the two may be transposed, the aorta arising from the right ventricle and the pulmonary artery from the left. The thoracic aorta may be double, the degeneration of the right side failing to take place, or the arch of the aorta may develop on the right side instead of the left. The large trunks which arise from the arch of the aorta are commonly three in number: innominate, left common carotid, and left subclavian, but several variations of their origins occur. At one extreme there are six separate trunks, right and left subclavians, vertebrals, and common carotids arising independently of each other, at the other extreme, all six arise as branches of a common trunk. The abdominal aorta is sometimes double, a persistence of the early embryonic paired vessels.

The veins are especially subject to variations. Double superior venae cavae sometimes occur because of the persistence of both right and left anterior and common cardinal veins, sometimes with a small anastomosing vessel between them, representing the left innominate vein. The inferior vena cava, together with the renal, suprarenal, azygos, and genital veins, is especially subject to variations, a fact which is not surprising in view of the complicated maze of vessels involved in the change from embryonic to adult conditions in that region of the body.

Figure 135 shows in a schematic manner the essential features of the three stages of circulation and furnishes a summary of the facts just presented. These drawings show the division of the heart into right

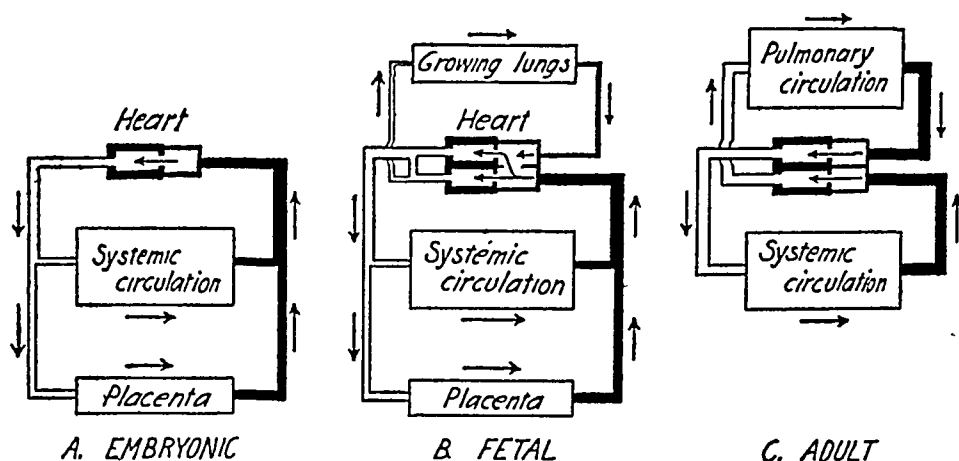


FIG. 135. Diagrams showing the three stages of human circulation. *A*, embryonic stage with single blood circuit, part of which goes to placenta. *B*, fetal stage; pulmonary circuit established, but incompletely separated from systemic circuit and carrying little blood. *C*, adult circulation with systemic and pulmonary circuits fully separated and carrying equal volumes of blood. Placental circulation eliminated.

and left sides and the establishment of the pulmonary and systemic circuits, incomplete in the fetal stage, but complete in the adult. They also show the elimination of the placental circulation.

E. ANOMALIES

The most striking anomaly of the circulatory system is absence or very poor development of the heart, a condition known as *acardiq*. This sometimes occurs in one of identical twins, the heart of the other twin being normal and supplying blood to the body of the acardic twin through anastomosing vessels of the common chorion of the two embryos. Thus the acardic twin is kept alive and sometimes develops to a considerable size, though usually in a badly deformed condition. The acardic condition cannot develop far in single pregnancies or in two-ovum twins, where a defective circulation quickly results in the death of the embryo.

A common defect is the failure of the foramen ovale to close after birth. This condition of itself, even if the opening is large, causes no serious inconvenience. Many persons with such an opening have lived comfortably to advanced age. If in addition to the open foramen ovale, however, there is at some point a stenosis (narrowing) of

soon coalesce to form a capillary network in which the larger lymph channels gradually develop, just as do blood vessels in the early vascular capillary plexus (Fig 116, p 164) These early lymph spaces soon make connections with embryonic veins, into which their contents drain

The Development of Lymphatics The earliest lymph capillaries form in very close relation to certain embryonic veins These first capillary networks soon condense to form six lymph sacs (1, 2) the jugular sacs, a pair which join with the internal jugular veins in embryos of about 18 mm (Fig 137A), (3, 4) the posterior sacs, a pair which join the bases of the primitive iliac veins in embryos of about 23 mm, (5) the retroperitoneal sac, ventral to the aorta in the base of the mesentery near the suprarenal glands, and (6) the cisterna chyli dorsal to the aorta at about the same level as the retroperitoneal sac (Fig 137A) The fifth and sixth sacs form about the same time as the posterior sacs

From the jugular sacs spread the lymphatics of the head, the neck, the thorax, and the arms, from the posterior sacs, those of the abdominal wall, the pelvis, and the legs, and from the retroperitoneal sac those of the abdominal viscera (Figs 136 and 137A) The lymphatics of these separate groups soon permeate the entire body and merge into a single system The spread of the lymphatics from the early sacs is accomplished by coalescence of newly formed endothelial spaces at the advance margins of the capillary plexus, but after this early phase of development the spread of lymphatics in the growing body is accomplished by terminal sprouting of the endothelial tubes

After the merging of the lymphatics into a single system, this entire system soon comes to drain into the veins through the two jugular sacs at the junction of the internal jugular and subclavian veins, inasmuch as the other sacs lose their connections with the veins (Fig 137B) The lymphatics from the anterior end of the body retain their symmetrical relations to the veins through the jugular sacs, but in the posterior region all the lymphatics become tributary to a single longitudinal vessel, the thoracic duct, which joins the veins through the left jugular sac In the development of this duct the retroperitoneal sac and the posterior sacs, together with their tributaries, establish drainage into the cisterna chyli (Fig 137B) At the same time a plexus of lymph channels, connecting the cisterna chyli with the jugular sacs, develops along the aorta (Fig 137B) From this plexus forms the thoracic duct

The thoracic duct is potentially double, with several cross vessels

CHAPTER XV

THE LYMPHATIC SYSTEM

A. GENERAL PLAN OF DEVELOPMENT

The Origin of Lymphatics. The lymphatic system is closely related, both anatomically and developmentally, to the blood vascular system. Lymph vessels begin their development in the sixth week, when the embryonic blood vascular system is already well established. Although the general developmental plan of the lymphatic system was clearly demonstrated during the early years of the present century, the question of the ultimate origin of lymphatics

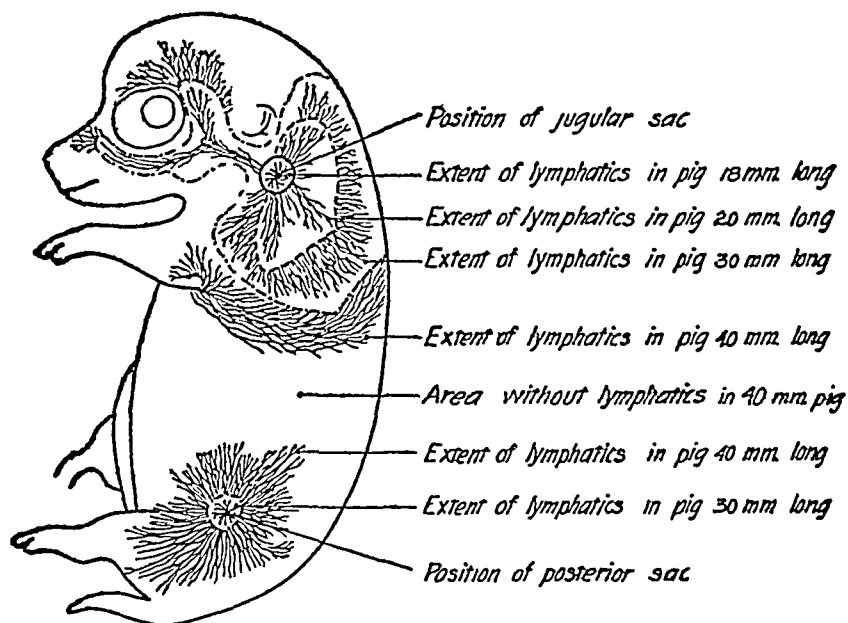


FIG 136 Composite drawing showing the spread of lymphatics in pig embryos between 18 and 40 mm long (Redrawn from Sabin in *Am Jour. Anat.*)

was more perplexing, and perhaps is not yet settled. To some workers it looked as if the lymphatics arose as outgrowths from veins, whereas to others it appeared that they arose independently. Though there are still advocates of both views, it seems safe to say that the great majority now believe that the first lymphatics are formed as numerous independent endothelial spaces which are produced by transformation of mesenchyme cells, just as are the earliest blood vessels. It is generally agreed that these early spaces, whatever their origin,

soon coalesce to form a capillary network in which the larger lymph channels gradually develop, just as do blood vessels in the early vascular capillary plexus (Fig 116, p 164) These early lymph spaces soon make connections with embryonic veins, into which their contents drain

The Development of Lymphatics The earliest lymph capillaries form in very close relation to certain embryonic veins These first capillary networks soon condense to form six lymph sacs (1, 2) the jugular sacs, a pair which join with the internal jugular veins in embryos of about 18 mm (Fig 137A), (3, 4) the posterior sacs, a pair which join the bases of the primitive iliac veins in embryos of about 23 mm, (5) the retroperitoneal sac, ventral to the aorta in the base of the mesentery near the suprarenal glands, and (6) the cisterna chyli dorsal to the aorta at about the same level as the retroperitoneal sac (Fig 137A) The fifth and sixth sacs form about the same time as the posterior sacs

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The thoracic duct is potentially double, with several cross vessels

connecting right and left channels. Usually only one duct, however, develops, formed from the posterior portion of the right channel, the anterior part of the left channel, and a vessel connecting the two (Fig. 137C). The thoracic duct is complete in embryos of about 30 mm. Thus it develops that the lymphatics from approximately three-fourths of the body join the veins on the left side, whereas the

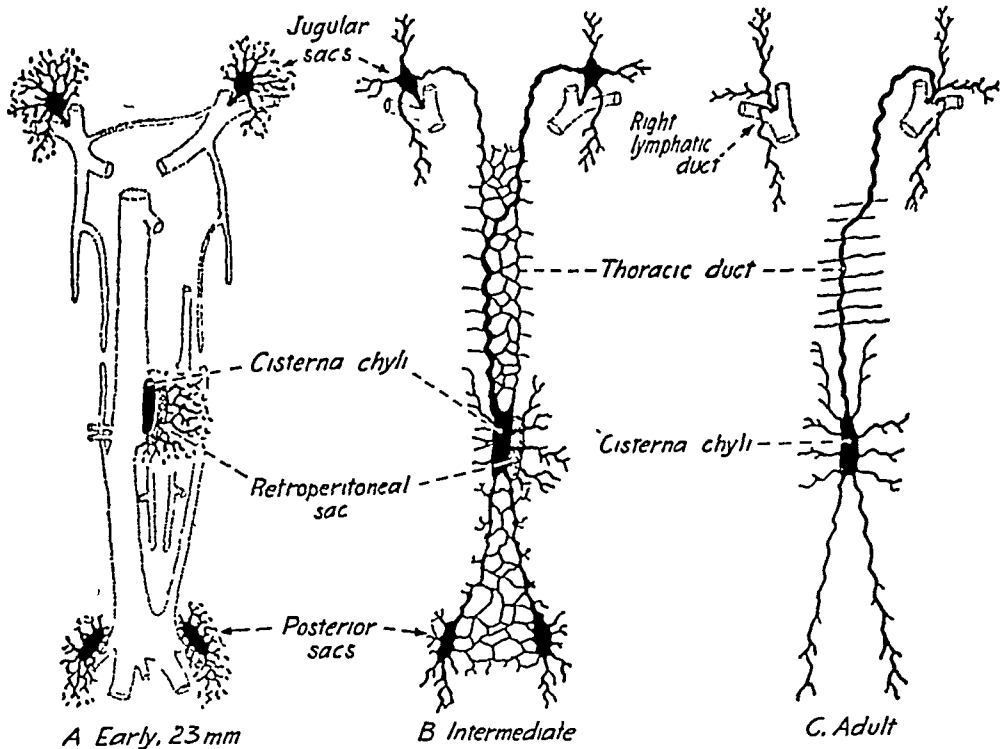


FIG. 137. Diagrams showing how the main channels of the lymphatic system form. A, the primary lymph sacs and early lymph vessels in relation to the veins of an embryo of 23 mm. B, an intermediate stage, showing the lymph sacs connected by the early plexus of lymph vessels. Double stage of thoracic duct. C, an advanced stage, showing how the thoracic duct is formed from the plexus.

remaining fourth, those tributary to the right jugular sac, enter through the right lymphatic duct (Fig. 137C). The lymph sacs, except the cisterna chyli, are temporary structures and during the fetal months are replaced by groups of lymph nodes.

It is of interest that the primary lymph sacs contain primitive blood cells which soon escape into the adjacent veins. Moreover, a variety of kinds of blood cells, including many erythrocytes, are produced in blood-forming centers in the wall of the thoracic duct, the process beginning in embryos of 30 mm. and continuing to the time of birth.

Other centers for the formation of blood cells, chiefly lymphocytes, are described below, even though not all of them belong strictly to the lymphatic system

The Lymph Nodes The first development of lymph nodes does not take place until the latter part of the third month. The first to develop are those in the axillary and inguinal regions and in the neck. Others develop later, both in fetal life and after birth. Lymph nodes may develop at any time during life almost anywhere in the body as the result of special activities or pathological conditions.

A lymph node has its beginning as a network or plexus of lymph vessels. In the meshes of this network are masses of mesenchyme from which develop the lymphoid tissue of the cortical nodules and medullary cords of the node. The lymph sinus of the node, connecting with afferent and efferent lymphatics, develops from the plexus of lymph vessels. Blood vessels have also been present in the mesenchyme of the region from the beginning and remain as the vessels of the node. The capsule and trabeculae are derived from the surrounding mesenchyme.

The Hemal Nodes The mode of development of the hemal nodes is in general similar to that of lymph nodes, except that they develop in relation to blood vessels instead of lymphatics.

The Spleen The beginning of the spleen is observed in embryos of 9 mm (nearly six weeks) as a swelling on the left side of the mesogastrium near the pancreas. Here the mesothelium of the mesogastrium becomes much thickened and gives off cells into the mesenchyme of the mesogastrium. At the same time the region becomes highly vascular. After this migration of cells the mesothelium soon returns to its original thin condition and the cells which have migrated from it are presumably the ones which, together with the invaded mesenchyme, produce the nodules, pulp, and trabeculae of the spleen. The organ grows in size and remains connected with the mesogastrium by only a narrow sheet of tissue. The blood vessels of the spleen form for some time a typical closed system but later take on the special characteristics of the adult spleen by the development of the venous sinuses and other characteristic structures. During fetal life the spleen is one of the important centers for the formation of blood cells, both leucocytes and erythrocytes.

B ANOMALIES

Lymphatics are subject to the same kinds of variations as are blood vessels and may be explained as different plans of emergence of larger

trunks from the early plexus of smaller vessels. Sometimes the thoracic duct joins the veins on the right side instead of the left, and sometimes it is double throughout. The duct frequently retains in varying forms the earlier plexus stage. The cisterna chyli is variable in size and position and may be wanting.

CHAPTER XVI

THE BLOOD CELLS

The development of blood cells is a matter that concerns not only the embryo but the adult as well, because the life of a blood cell is short and new ones must continually be produced to keep up the supply. Except in young embryos, blood cells do not multiply in the blood stream but are developed from primitive cells in certain organs, known as **hemopoietic** (blood-forming) **organs**. Several blood-forming organs function at successive times during life.

(1) The earliest blood cells develop in *blood islands* in the splanchnic mesoderm of the *yolk sac*, as described on page 163. These centers become active about the beginning of the fourth week. (2) The early blood cells of primitive type multiply by mitosis in the *blood stream* of young embryos. (3) Some blood cells develop from the *endothelium* of the vessels during the early weeks. (4) For a period beginning about the sixth week, the *liver* serves as the most important blood-forming organ. It decreases in importance after the middle of prenatal life but continues to be somewhat active until birth. (5) From the second or third month until birth, the *lymphoid organs* (spleen, lymph nodes, and thymus) produce all kinds of blood cells, but after birth they produce normally only lymphocytes and monocytes. (6) *Bone marrow* serves as the outstanding tissue for the formation of all kinds of blood cells from the time of its first appearance about the seventh week. After birth it is the only normal source of erythrocytes and granular leucocytes. It also produces a few lymphocytes.

In all locations where blood cells form, both before and after birth, the general mode of formation is the same. Mesenchyme cells (or connective tissue cells derived from mesenchyme) round up and become stem cells (hemoblasts). In the early yolk sac these cells become detached as the primitive blood cells. They resemble large lymphocytes (Fig. 138A). Blood formation in the embryo itself begins by the production of hemoblasts from mesenchyme cells. Their production continues throughout life, and from these stem cells all the kinds of blood cells are derived. Each kind of blood cell develops

characteristically, development being accomplished during several successive cell divisions, with each cell generation marking progress toward the final type.

The blood-forming organs (spleen, lymph nodes, thymus, and marrow) all have the same essential histological structure, namely, a stroma of reticular tissue in the meshes of which are many rounded cells, representing various stages in the development of the blood cells. Such development, except in the very earliest embryonic stages, is accomplished in this tissue outside the vessels. The completed cells penetrate the thin walls into the blood or lymph stream. In the liver, which differs from the general type of hemopoietic organ, the hemoblasts are formed from connective tissue cells between the epithelial liver cells and the endothelium of the sinusoids. At the height of its hemopoietic activity the blood-forming cells far outnumber the liver cells.

The Development of Erythrocytes. The development of erythrocytes from the primitive stem cells involves three main changes: (1) the production of hemoglobin, (2) the formation of a stout cell membrane, and (3) the loss of the nucleus (Fig. 138).

In this development there are two preliminary stages between hemoblasts and erythrocytes, representing different cell generations, making four stages in all: (1) **Hemoblasts** (Fig. 138A). (2) **Megaloblasts**, cells having a definite cell membrane and a little hemoglobin in the cytoplasm. The nucleus is relatively smaller than in the preceding stage and stains more deeply (Fig. 138B). Until about the sixth week megaloblasts are the only kind of red blood cells to develop; after this time they become relatively fewer and during the third month practically disappear from circulation, though they continue to be found throughout life as a developmental stage in the marrow. (3) **Normoblasts** which differ from megaloblasts in having more hemoglobin and a smaller and denser nucleus (Fig. 138C). They appear in the blood during the sixth week and at two months are the most abundant kind, but after the seventh month they practically disappear, persisting only as a developmental stage in the marrow. (4) **Erythrocytes** (mature red blood cells) are formed from normoblasts by loss of the nucleus (Fig. 138D). There is a difference of opinion as to how the nucleus is lost; some believe that it is absorbed, others that it is extruded.

The earliest erythrocytes appear toward the close of the second month, being formed first in the liver. During the third month they become the most abundant form; and by the time of birth all the nucleated, primitive types have disappeared from the circulation.

The Development of Leucocytes All the kinds of leucocytes develop from the same kind of stem cell (hemoblast) as do erythrocytes (Fig 138A) Their development, however, follows an entirely different pattern, inasmuch as leucocytes retain the nucleus, become amoeboid, and have colorless cytoplasm

The lymphocytes remain closest to the parent stem-cell type Monocytes show a little more differentiation and are probably a further development of lymphocytes These two constitute the lymphoid series, being produced in lymph nodes and the spleen of

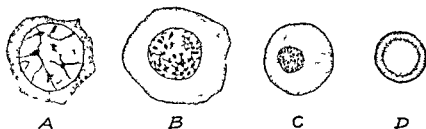


FIG 138 Four stages in the formation of erythrocytes A, hemoblast B, megakaryoblast C, normoblast D, erythrocyte (Drawings of individual cells selected from colored plates of Maximow in *Arch f mikr Anat*)

the adult The granulocytes (polymorphonuclear leucocytes) attain a higher differentiation, both as to the elaborate shape of the nucleus and the specialized granules in the cytoplasm Each of the three kinds (neutrophil, acidophil, and basophil) is characterized by special development of the nucleus and the cytoplasmic granules On account of their abundance, granular leucocytes in developmental stages are conspicuous elements in the marrow, being known as **myelocytes** On the whole, the history of the leucocytes during prenatal life is not well known, and little can be said about either the exact mode of development or the time of first appearance of the different kinds All the types, however, are present at birth

The development of Blood Platelets Blood platelets are not generally regarded as cells At the present time the most widely accepted view of their nature and origin is that they are fragments of cytoplasm without nuclear material, which have separated from the tips of the pseudopods of the giant cells or megakaryocytes of red marrow (Fig 139) The megakaryocytes also are derivatives of hemoblasts, from which they are produced by repeated incomplete divisions of the nucleus and continued growth of the cytoplasm, which does not divide They are never normal, free elements in the blood In adult life they are found only in the marrow, but before birth they

are present in the liver and spleen while these organs are acting as general blood-forming organs.

Though there has been much careful study upon the development of blood cells, many points of uncertainty still remain, and the reader of more extensive textbooks may become confused by involved discussions concerning the relative merits of the monophyletic, dualistic, and polyphyletic theories. Though all authorities accept the general plan as presented above, there is division of opinion as to

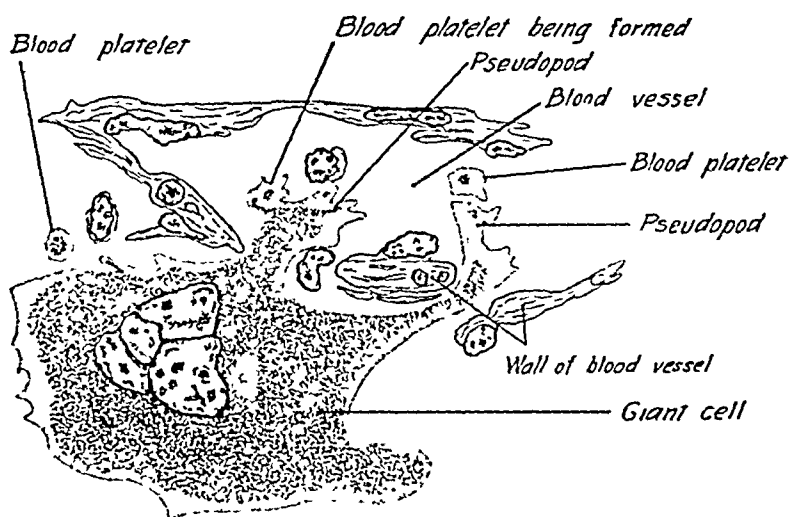


FIG 139. The formation of blood platelets. A giant cell in the marrow of a kitten is shown extending two pseudopods into a blood vessel through openings in the wall. Platelets are seen in process of being separated from these pseudopods (Redrawn from Wright in *Jour. Morph.*)

whether the different types of blood cells come from one single kind of stem cell or from two or more types which resemble each other very closely in appearance. For all practical purposes, however, the account given in this chapter includes the points upon which there is general agreement; the uncertainty concerns the obscure beginnings of the diversification process.

CHAPTER XVII

THE UROGENITAL ORGANS

The urogenital organs include two systems of organs with wholly different functions, but the two are so closely related anatomically that it is impossible to study one and at the same time ignore the other. Embryologically they are even more intimately related, a fact which will be more fully appreciated after the detailed study of their development.

In the development of both excretory and reproductive organs mesoderm plays the major part, but entoderm and ectoderm also make important contributions.

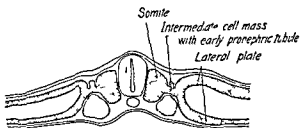


FIG 140 Cross-section through 33 hour chick embryo to show position of intermediate cell mass (nephrotome) between somite and lateral plate

A THE KIDNEYS AND THEIR DUCTS

During development there occur in succession three kidneys, the pronephros, the mesonephros (Wolffian body), and the metanephros, the last of which is the permanent kidney. All three kidneys and their ducts originate from the intermediate cell mass or nephrotome (Figs 50, p 79, and 140). The intermediate cell mass, from the time of its first formation, lies closely adjacent to the wall of the developing coelom (lateral plate) (Fig 140). It will be seen in the following pages that this anatomical proximity persists throughout development of the three kidneys and their ducts and of the gonads as well, so that the student must be constantly alert to avoid confusion between the parts derived from the coelom wall and the intermediate cell mass.

1 The Pronephros

The pronephros develops and degenerates very early in embryonic life. It is seen first in embryos of about 1.7 mm (fourth week) and has almost disappeared in embryos of 4.25 mm. Its whole duration covers about one week. The pronephros develops from the anterior end of the nephrotome in segments 7-14 (lower cervical and upper thoracic

regions). Each pronephros consists of about twelve tubules connecting to the pronephric duct. The anterior tubules develop first and have already degenerated before the posterior ones form. The tubules arise as outgrowths of the nephrotome (Fig. 140). At one end the tubules open into the coelom, and at the other end they fuse to form the anterior end of the pronephric duct. The duct then grows caudad from the pronephros through the nephrotome by an independent growth. It lies just beneath the coelom wall and makes connection with the cloaca in embryos of about 4.2 mm. The human pronephros is not a functional kidney; but when the tubules degenerate, the duct persists to play an important part in later embryonic development and in adult life (Fig. 146).

2. The Mesonephros or Wolffian Body

The mesonephros develops a little later than the pronephros from the middle part of the intermediate cell mass (segments 10-26),

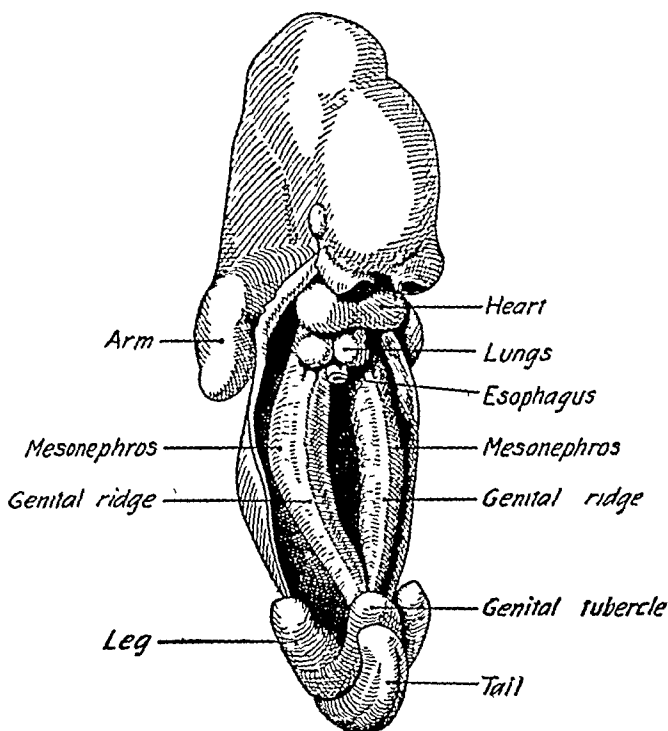


FIG. 141. Ventral dissection of human embryo 9 mm. long (about 5½ weeks), showing the mesonephros and the genital ridges from which develop nearly all the parts of the excretory and reproductive organs. (Redrawn from Kollmann's *Handatlas*.)

extending throughout the length of the thorax and over about three lumbar segments. It is a much larger organ than the pronephros. Each

organ includes about eighty-three tubules, though not more than about forty are present at any one time, those toward the anterior end undergoing degeneration before those at the posterior end have formed. The two mesonephroi soon become a prominent pair of longitudinal ridges bulging into the coelom (Figs 141 and 144A).

The mesonephros begins to develop in embryos of 2.5 mm (four weeks), while pronephric tubules are still present. It very quickly attains its greatest development and is already undergoing rapid degeneration in embryos of 10–12 mm (six weeks). In embryos of 21 mm (seven and one-half weeks) about twenty-six tubules are left at its caudal end, which persist and take part in the development of the male genital ducts.

The tubules of the mesonephros develop from the mesoderm of the intermediate cell mass, each tubule appearing first as a solid mass, which later acquires a lumen and becomes an elongated, convoluted tube. Each tubule forms a union with the pronephric duct, which now becomes the mesonephric or Wolffian duct. Into the free end of each tubule a glomerulus of capillaries invaginates. Thus there are formed renal corpuscles very similar to those of the permanent kidney (Fig 144A).

3 The Metanephros or Permanent Kidney

The metanephros has a double origin. The ureter, pelvis, calyces, and collecting tubules arise from an outgrowth of the Wolffian duct, whereas the secreting parts of the tubules are formed directly from the posterior end of the intermediate cell mass. The manner of development is as follows.

The earliest rudiment of the kidney is a bud which appears on the dorsal side of the Wolffian duct near its entrance to the cloaca in embryos of about 5 mm (five weeks). This bud elongates into a tube which grows cephalad and shortly enlarges at its tip into the primitive renal pelvis (Fig 142A). The unexpanded part of the tube becomes the ureter (Fig 142A, B, and C). The primitive pelvis soon becomes bilobed, and from each lobe there grow out four to six tubules which elongate somewhat and in turn branch, giving rise to numerous tubules, and these to others in successive branchings, until about twelve divisions have occurred. Thus, by the fifth month, a very thickly branched, tree-like structure is present.

The pelvis and calyces of the adult kidney develop by expansion of the primitive pelvis and absorption into it of the tubules of the first four generations, and the papillary ducts and collecting tubules develop from the numerous branching tubules of the later generations.

While the outgrowth from the Wolffian duct is still unbranched (in embryos of about 7 mm.), its anterior end comes into contact with the posterior end of the intermediate cell mass, which forms a cap of nephrogenic (kidney-forming) tissue over the growing end of

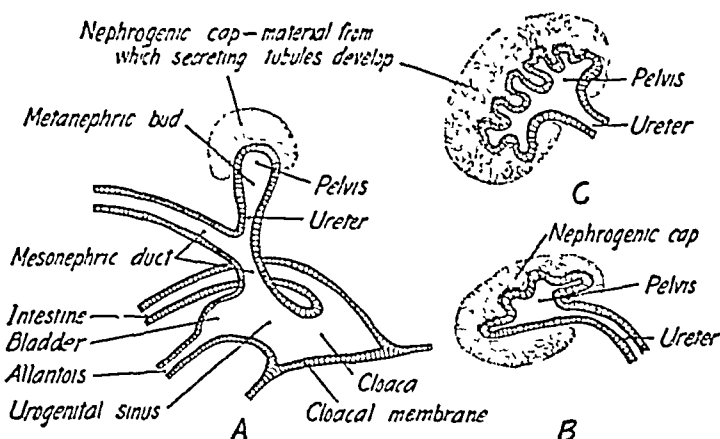


FIG. 142. Diagrams of three early stages in the development of the metanephros or permanent kidney. *A*, shows cloaca and associated structures, including metanephric bud arising from the mesonephric duct, and the nephrogenic cap at the tip of the bud. *B* and *C*, later stages, showing the branching of the renal pelvis to form the beginnings of the collecting tubules. (Adapted from Keith's *Human Embryology and Morphology*, Edward Arnold and Co., London.)

the tube (Fig. 142). At each successive division of the tube, this cap divides also, so that a mass of this tissue lies close to the distal end of each tubule. At appropriate times these masses develop into the secreting parts of the tubules as follows.

The nephrogenic masses are at first solid and approximately spherical (Fig. 143*A*). Then each develops a lumen and becomes an elongated tubule of epithelium which unites at one end with the tip of the collecting tubule (Fig. 143*B*). The tubules continue to elongate and to become more convoluted until the adult form is attained (Fig. 143*C*). The free end of each tubule expands to become **Bowman's capsule**, while a mass of mesenchyme containing capillaries (a **glomerulus**) comes into relation with the capsule and produces the **renal corpuscle**. The first renal corpuscles develop during the second month, and new ones continue to develop until after birth.

The **fibrous capsule** surrounding the kidney and other supporting tissues of the kidney develop from mesenchyme surrounding the growing tubules. During the development of the kidney the tubules become arranged in groups corresponding to the adult **renal papillae**, and at the same time corresponding grooves, which indicate lobes,

appear on the exterior of the organ. This lobulated condition arises about the tenth week and persists until after birth (Fig 153)

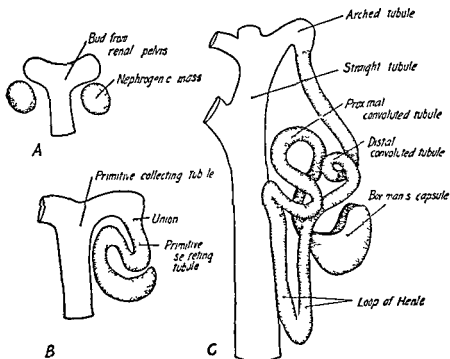


FIG 143 Diagrams showing the development of the individual tubules of the kidney. Parts of tubule developing from nephrogenic mass are shaded, parts from metanephric bud, unshaded. A, early stage before the union of the two parts. B, shortly after union of parts. The secreting tubule has become S-shaped. C, the tubule has assumed the general form of the mature tubule (Redrawn from Huber in *Am Jour Anat*)

4 The Function and Importance of the Three Sets of Excretory Organs

The metanephros is the functional adult kidney in reptiles, birds, and mammals, as is the mesonephros in fishes and amphibians. The pronephros forms part of the functional kidney in the cyclostomes and is presumed to represent the kidney of extinct ancestral forms.

It will readily be recognized that the embryo as well as the adult must carry on excretion. In reptiles and birds the mesonephros and metanephros in succession produce concentrated urine which is stored until hatching in the large, saccular allantois. In mammals, however, the placenta has become an effective prenatal excretory organ. In it the waste products of fetal metabolism pass from the fetal blood into the maternal blood, to be eliminated through the mother's.
 Nevertheless, some rather recent studies have shown that in

all groups of mammals both the mesonephros and metanephros secrete urine during the prenatal months, though this urine is not large in amount or, of high concentration. It is discharged into the allantois, the bladder, or the amniotic cavity, but from these cavities it is resorbed and finally is excreted through the placenta, even in species with an epithelio-chorial placenta. The kidneys are thus functioning in prenatal life, and there is no radical or sudden change at birth when the placenta is lost.

In this connection it has been observed that up to the time of birth the visceral layer of the capsular epithelium surrounding the renal glomerulus is of the columnar type and tightly invests the capillary loops in such a way that the filtering action of the kidney would probably of necessity be slow. About the time of birth, however, this tall epithelium begins to break up and the capillary loops to loosen. The tall epithelium is then gradually replaced by the usual flat cells, which closely invest each individual capillary of the glomerulus, this process being completed about the age of two years.

Until very recently there has been a rather general belief that the prenatal kidneys are important excretory organs in species with a large allantoic sac and less intimate placental union (horses, cattle, swine, cats, dogs) and that the fetal urine is stored in the large allantois until birth, as it is known to be in birds before hatching. It has also been a general belief that in species with an intimate placental union and a small allantois (man, primates, rabbit, rat) the prenatal kidneys either do not secrete urine at all or do so in very small quantities. It would seem, however, from more recent evidence that neither view is wholly correct; more probably in all species the prenatal kidneys function, but their secretion is not important, inasmuch as the fetal urine is finally eliminated through the placenta.

B. THE REPRODUCTIVE GLANDS AND THEIR DUCTS

The reproductive system affords the one striking example of organs that are different in the two sexes, for which reason the study of their development reveals some points of special interest. It will be seen from the following pages that the organs of the two sexes are very similar at their beginning, and that the sexual peculiarities arise by differential development of the seemingly indifferent rudiments.

The reproductive organs, unlike those of circulation, excretion, and other functions, are very slow in developing to the point where they are capable of carrying on their special function, the reproductive power being delayed until the time of puberty, several years after

birth It is worthy of note, however, that the reproductive glands do exercise another function at a time quite early in embryonic life, namely, the production of an internal secretion or hormone which exercises an important influence in regulating the development of certain parts of the body

1 The Reproductive Glands

The Origin of the Reproductive Glands The ovary and the testis have a similar embryonic origin, and up to a certain point one cannot be distinguished from the other The earliest primordia of the sex glands appear in embryos of about 5 mm (five weeks) At this age the mesonephros have attained a good size and form two ridges bulging into the coelom (Fig 141)

The primordia of the sex glands (gonads) form by proliferation of a strip of peritoneal epithelium (developed from the lateral plate) along the ventro-median surface of each mesonephros, the process beginning in embryos of about 6 mm The multiplying epithelial cells grow inward into the mesonephros, but the growth also causes an expansion into the coelomic cavity, the genital ridge (Figs 141 and 144A) The inner epithelial mass very soon becomes subdivided into numerous cell columns, the sex cords, connected to the superficial germinal epithelium from which they are growing (Fig 144A) Continued proliferation and specialization of the germinal epithelium and the sex cords produce all the parts of the sex glands, including both the connective tissue and the epithelial portions In the sex cords two chief kinds of epithelial cells are soon seen numerous small, rounded cells and, among them, some larger, rounded cells called by some writers genitaloid cells and by others primordial germ cells

The genital ridges are the indifferent gonads From them develop by appropriate specialization the ovaries and testes Each gonad is at first as long as the mesonephros (Fig 141), but as it grows thicker it shortens, until it has the compact form of the mature organ As the genital ridge grows more prominent, it becomes separated from the mesonephros by deepening lateral grooves, until it is suspended only by a mesentery-like, double layer of peritoneum, the mesorchium or mesovarium, according to the sex (Figs 144, 150, and 151)

Sex Differentiation It is now generally recognized that in the development of the gonads there are *two* successive proliferations of epithelium from the germinal epithelium The first one, which has just been described, produces the primary sex cords, it occurs alike in both sexes In the male it gives rise to the functional part of the testis In the female the primary cords in the ovary degenerate The

second proliferation, producing the secondary sex cords, is of importance in the female, where these cords develop into the cortex of the ovary. As the secondary sex cords push inward, they crowd the primary cords into the medulla of the ovary, where they degenerate. In the male the secondary cords either do not form at all or else form only slightly.

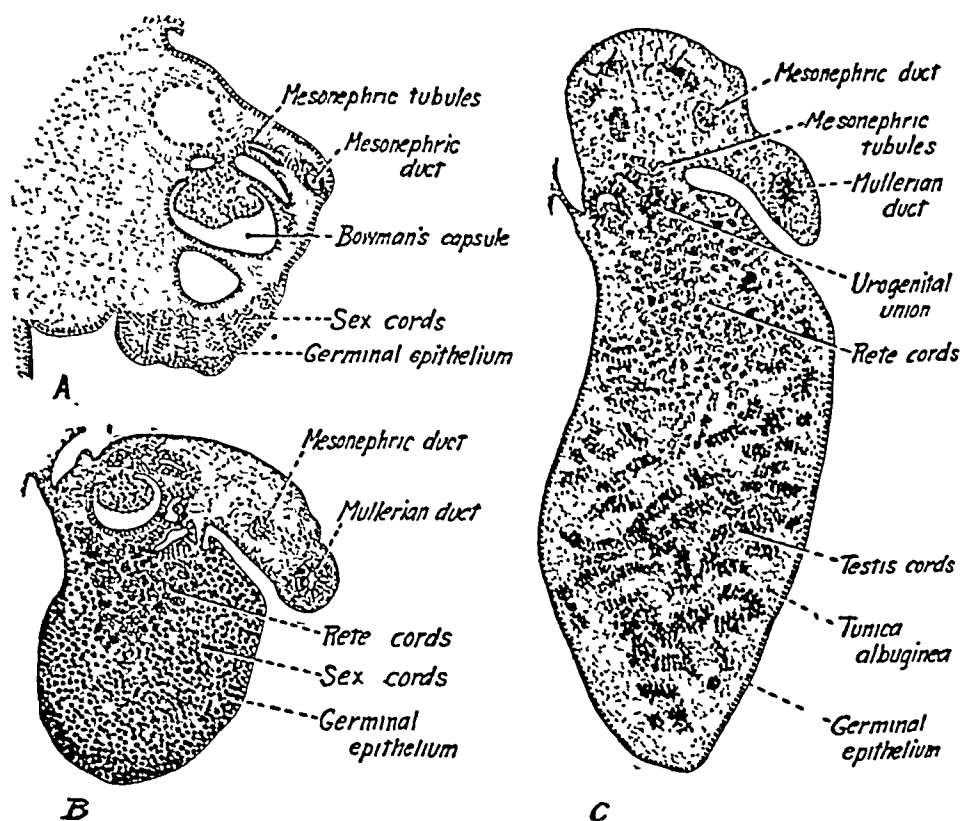


FIG. 144. Sections through human genital ridge showing relation to mesonephros. All drawings approximately $\times 60$. Show growth of gonad and reduction of mesonephros. A. Eleven mm. embryo. Shows growth of sex cords toward mesonephros. (Modified from Felix in Keibel and Mall, *Human Embryology*.) B. Female embryo, 21 mm. Shows indifferent condition, whereas in male of same age, differentiation of testis is plainly seen. C. Male embryo, 28 mm. The urogenital union does not actually occur until a later time, but its position is shown in this figure. (B and C adapted from Wilson in *Cont. to Emb.*, Carnegie Inst, Washington.)

The Differentiation of the Testis. During the seventh week, two characteristic features, by which the male gonad may be recognized as a testis, appear rather suddenly: (1) The tunica albuginea, a stout layer of connective tissue, develops just beneath the germinal layer of epithelium, separating it permanently from the underlying sex cords (Fig. 144C). This connective tissue develops by transformation of

epithelial cells in the portions of the sex cords just beneath the germinal epithelium (2) The primary sex cords assume the form of very definite testis cords with branchings and anastomoses The testis cords are separated from each other by the less compact stroma, which likewise is a derivative of the epithelial mass

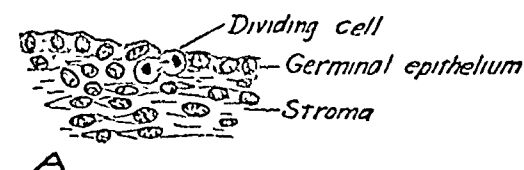
After the formation of the tunica albuginea, the germinal epithelium again becomes a flat mesothelium, it is of no importance in relation to the testis except as the visceral layer of the tunica vaginalis In the early testis the testis cords radiate from the mediastinum at the base of the mesorchium toward the general surface of the organ (Fig 144C) The testis cords differentiate into these three types of tubules connected in series (1) By far the greater length of the tubules becomes the convoluted seminiferous tubules (2) A much shorter portion, close to the mediastinum, becomes the tubuli recti (3) The deepest part, lying in the mediastinum, becomes the rete testis, of richly branching and anastomosing cords (Fig 144C) In embryos of about 78 mm the cords of the rete testis make connection with some of the persisting tubules of the mesonephros and so form the outlet for the testis through the Wolffian duct (Fig 146C and E) This junction is the urogenital union (see also p 213) All the testis cords are at first solid, but they gradually become hollow tubules, lumen formation beginning in the rete testis at the thirteenth week and in the convoluted tubules about the seventh month The process is not yet complete at birth

In the development of the tissue structure of the seminiferous tubules, some authorities hold the opinion that the spermatogonia develop from the primordial germ cells, whereas others believe that these cells degenerate early and that both spermatogonia and cells of Sertoli develop from the smaller cells of the testis cords Both the connective tissue septa and the more delicate connective tissue among the tubules, as well as the epithelial interstitial cells, develop from the stroma between the tubules

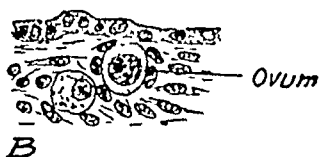
During its development the testis undergoes an extensive change in position known as descent, it migrates from its original position in the lumbar region into the scrotum (Figs 152 and 153) A fuller account of the descent of the testis is given on p 219

The Differentiation of the Ovary In its earlier phases the ovary differentiates more slowly than the testis The primary sex cords, instead of producing sharply delimited strands of cells, break up into small, irregular masses, each containing both small cells and primordial germ cells In the third or fourth month, however, the second proliferation begins, which continues until the sixth month The

secondary sex cords so produced gradually crowd the primary cords into the medulla, where they degenerate by about the eighth month. Before the primary cords degenerate, there forms from their deepest



A



B



C



D

FIG. 145. Four figures chosen to show the formation of young ova in the adult mouse by division of cells in the germinal epithelium covering the ovary. *A*, a cell in division, one of its daughter cells being given off underneath the germinal epithelium to which the parent cell belonged. *B*, a young ovum immediately beneath the germinal epithelium. *C*, a young ovum separated from the germinal epithelium by one layer of stroma cells. *D*, a young ovum surrounded by follicle cells. (Outline drawings made from photomicrographs published by Edgar Allen in *Am. Jour. Anat.*)

portion a rete ovarii, which makes an imperfect urogenital union with the mesonephric tubules, even though it is of no importance and later degenerates (Figs. 144*B* and 146*C*). From the growing secondary cords the ova and follicle cells of the cortex of the ovary develop.

The tunica albuginea in the human ovary does not form until about the sixth month. It develops from an invasion of connective tissue from the hilus of the ovary which penetrates the cortex and spreads out under the germinal epithelium. After the formation of the tunica albuginea, the germinal epithelium remains thicker than in the testis, and small groups of cells continue to migrate from it into the underlying cortex. The connective tissue stroma of the ovary and the theca of the follicles develop from the epithelial masses of the first and second proliferations.

The Origin of the Germ Cells.

In the study of the developing gonads there has for many years been great interest in the origin of the cells which are to become ova and spermatozoa. In spite

of careful study on many species of animals, however, much difference of opinion still exists on certain points.

At one extreme are those who hold that the primordial germ cells in the sex cords of the early gonads do not originate in the germinal epithelium but are set apart much earlier, remote from the future

genital ridge in the entoderm, whence they migrate into the ridge when it is formed. These investigators believe that these cells, and they alone, are the ancestors of the functional ova and spermatozoa.

On the other hand, there are those who insist that all the primordial germ cells degenerate and that the functional germ cells originate by transformation of peritoneal cells in the germinal epithelium. In the testes, regardless of the source of the germ cells, it is obvious that migration from the germinal epithelium into the organ ceases with the formation of the tunica albuginea and that all the future spermatozoa are produced by continued multiplication of cells already in the seminiferous tubules. In the ovary, on the other hand, most students are agreed that the tunica albuginea does not prevent the migration of cells from the germinal epithelium into the cortex of the ovary. For many years it was rather generally believed that the migration of ova from the germinal epithelium is confined to the earlier developmental months and that at birth the cortex of the ovary contains all the ova there ever will be. During more recent years, however, there has been a growing body of evidence that the proliferation of ova from the germinal epithelium continues during the years of fertility and that, indeed, the supply of ova during these years is wholly dependent upon such migration of ova (Fig 145). It seems safe to say that this is the view most generally accepted for many species of mammals, including man, but difference of opinion still exists as to whether the ova are produced by transformation of cells of the germinal epithelium or are derived from primordial germ cells which have found lodgment in the epithelium.

2 The Ducts of the Reproductive Glands

Two different embryonic ducts are involved in the development of the adult genital ducts: (1) the mesonephric ducts (Wolffian ducts), which become the genital ducts of the male, and (2) the Mullerian ducts, which become the genital ducts of the female. Both these ducts develop alike in males and females until about the beginning of the third month, when the Mullerian ducts begin to degenerate in the male and the Wolffian in the female. There is thus an indifferent stage of the genital ducts as well as of the genital glands. It should be recognized that, although the ovary and testis are exactly comparable organs, having identical embryonic origins, the male and female ducts have different origins. The developmental history of these ducts, as well as of other parts of the urogenital organs, is shown diagrammatically in Fig 146 and in somewhat less diagrammatic manner in Figs 149, 151, and 152.

The Origin and the Fate of the Mesonephric Ducts. It has already been learned that the mesonephric ducts belong primarily to the urinary system, being developed as the excretory ducts of the two

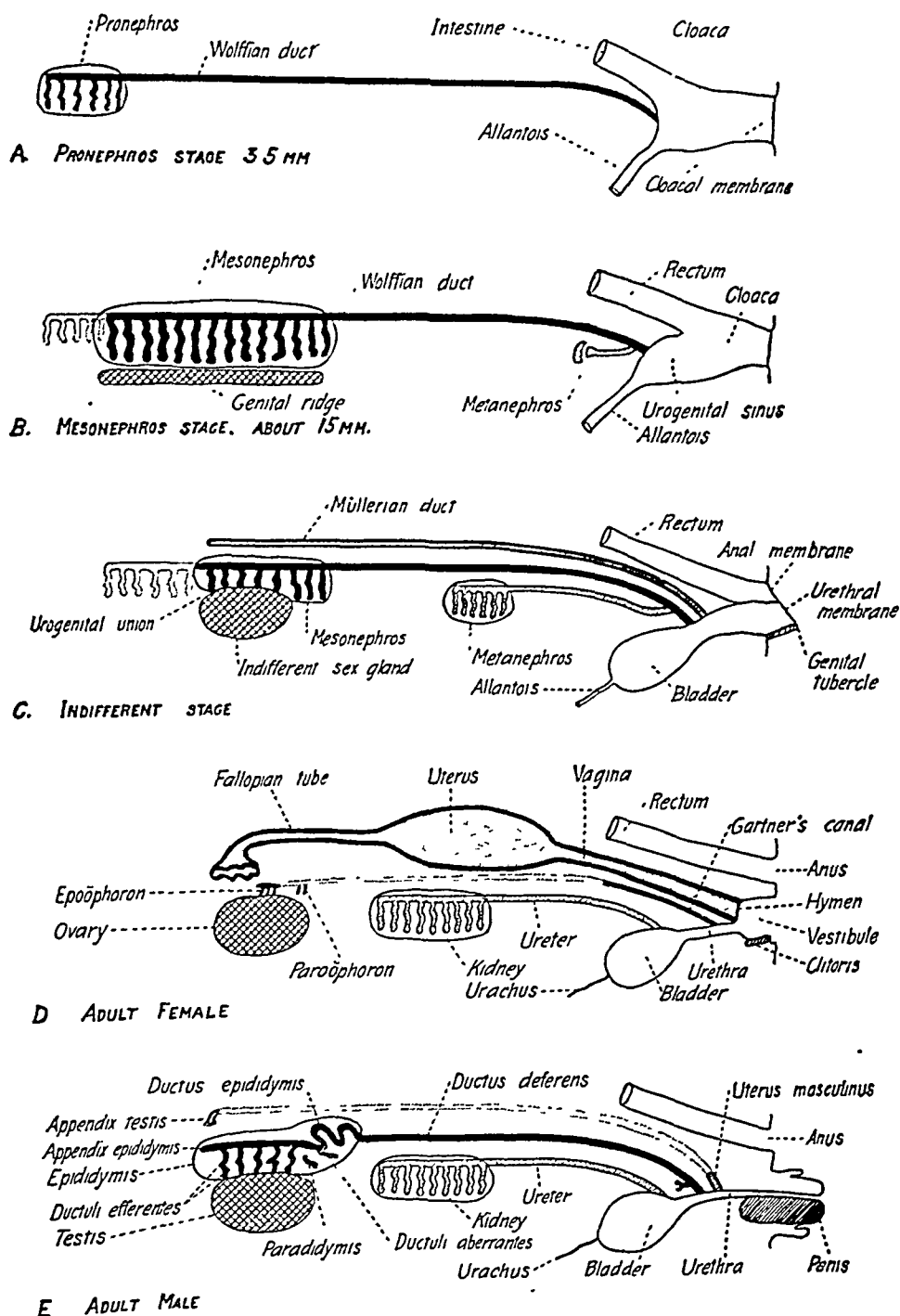


FIG. 146. Five diagrams showing the transformation of the three sets of kidneys, the urogenital ducts, and the cloaca during the development of both sexes.

embryonic kidneys. When the mesonephros degenerates, not only the mesonephric duct but also about twenty-six tubules at the posterior end of the organ persist (Fig 146B and C). In both sexes the rete cords of the genital ridge come into intimate union with five to twelve of these persistent mesonephric tubules at the cephalic end of the series. This union occurs in embryos of about 78 mm CR length and is known as the urogenital union (Fig 146C). The subsequent history of the urogenital union is very different in the two sexes.

In the male the mesonephric tubules which have made connection with the rete testis become the efferent ducts (ductuli efferentes) in the globus major of the epididymis (Fig 146E). The mesonephric duct, into which these open, becomes the sperm duct, the part near the testis becoming much coiled as the ductus epididymis, while the remainder becomes the ductus deferens, which discharges into the urethra just below the bladder (Fig 146E). The terminal part of the duct becomes the ejaculatory duct, and the seminal vesicles arise as outgrowths from the duct just short of the end. Thus the ducts originally developed in connection with the urinary organs become secondarily connected with the male reproductive organs, which they serve as genital ducts. These facts may be summarized by saying that the persistent part of the mesonephros becomes the globus major of the epididymis, and its duct becomes the globus minor and the sperm duct (See Table 5, p 214).

A few of the persistent mesonephric tubules do not become involved in the urogenital union, but persist in the adult as vestigial structures of no known function, the paradidymis and ductuli aberrantes, the blind cranial end of the mesonephric duct persists as the appendix of the epididymis (Figs 146E and 153).

In the female no functional organ develops from the remnants of either the mesonephros or the mesonephric ducts, but certain vestiges persist. From the mesonephric tubules which unite with the rete ovarii comes the epoophoron (corresponding to the epididymis), and from the tubules which do not make this union, the paroophoron. Sometimes a portion of the mesonephric duct persists as Gartner's canal, which lies in the wall of the uterus and vagina (Figs 146D and 151). The degeneration of the mesonephric duct in the female begins about the ninth week.

The Origin and Fate of the Mullerian Ducts The female ducts, unlike those of the male, are not part of the urinary system, but develop independently and serve no purpose except that of female genital ducts. The Mullerian ducts begin to develop in embryos of about 10 mm, when the mesonephros is at its greatest development.

Each duct begins as an ingrowth of the *peritoneal epithelium* covering the mesonephros near its anterior end. This ingrowing mesothelium forms a short groove which becomes deeper and sinks beneath the surface as a tube. Its anterior end is the first part to form and opens into the peritoneal cavity as the *ostium abdominalis*

TABLE 5

HOMOLOGIES OF UROGENITAL ORGANS

Indifferent	Male	Female
Genital ridge	<i>Testis</i> Mesorchium Gubernaculum (part)	<i>Ovary</i> <i>Mesovarium</i> <i>Ovarian ligament</i>
Mesonephros	Appendix epididymis <i>Efferent ductules</i> <i>Ductus epididymis</i> Paradidymis Ductuli aberrantes	<i>Epoöphoron</i> <i>Paroöphoron</i>
Mesonephric duct	<i>Ductus deferens</i> <i>Seminal vesicles</i> <i>Ejaculatory ducts</i>	Gartner's canal
Müllerian duct	Appendix testis	<i>Uterine tubes</i> <i>Uterus</i>
Vesico-urethral primordium	Prostatic utricle <i>Bladder</i> <i>Prostatic urethra</i> (part)	<i>Vagina</i> <i>Bladder</i> <i>Urethra</i> (entire)
Urogenital sinus	<i>Prostatic urethra</i> (part) <i>Membranous urethra</i> <i>Cavernous urethra</i> <i>Prostate gland</i> <i>Bulbourethral glands</i>	<i>Vaginal vestibule</i> (part) <i>Vaginal vestibule</i> (part) <i>Vaginal vestibule</i> (part) <i>Paraurethral glands</i> <i>Vestibular glands</i>
Labio-scrotal swellings	<i>Scrotum</i>	<i>Labia majora</i>
Urethral folds	<i>Penis</i> (part)	<i>Labia minora</i>
Genital tubercle	<i>Penis</i> (part)	<i>Clitoris</i>
Inguinal fold	Gubernaculum (part)	<i>Round ligament</i>

of the tube. From this beginning, the duct, by independent growth at its tip, grows caudad beneath the peritoneum and parallel to the mesonephric duct, until in embryos of about 24 mm. (eight weeks) it reaches the urogenital sinus, where it ends blindly, closely adjacent to the mesonephric ducts, in an elevation known as **Müller's tubercle**.

The two Müllerian ducts are at first separate throughout their course, but about the time they reach the urogenital sinus their caudal portions unite to form the utero-vaginal canal, while the cephalic portions remain separate (Fig. 149).

In the female the uterus and vagina develop from the utero-vaginal canal, and the two uterine tubes (Fallopian tubes) from the

separate portions of the Mullerian ducts (Figs 146D and 151) In this development there forms about the duct, especially the utero-vaginal portion, a dense mass of mesenchyme, from which develop the muscular and fibrous parts of the organs The epithelial lining of these organs develops from the Mullerian ducts except in the lower portion of the vagina (possibly its entire length), where recent studies have shown the lining to be formed of entodermal epithelium migrating from the urogenital sinus and replacing the original mesodermal lining Nevertheless, the vagina is fundamentally derived from the Müllerian ducts The vagina for a time has a solid core of epithelium, in which, at about eighteen weeks, the lumen begins to form by breaking down of the central cells, the stratified squamous lining being left The fimbriated ostia of the uterine tubes develop from the primitive ostia of the Mullerian ducts The hymen makes its appearance as a fold on the wall of the vagina at its external opening at the position of Muller's tubercle (Fig 146D)

In the male the Mullerian ducts develop as in the female until the ninth week, about which time they begin to degenerate In the adult male only two vestiges of the Mullerian ducts persist, the *vagina masculina* (uterus masculinus or prostatic utricle), which represents the vaginal part of the tube, and Morgagni's appendage of the testis, which corresponds to the abdominal ends of the uterine tubes (Figs 146E and 152) (See Table 5)

C THE URINARY BLADDER AND THE URETHRA

As was pointed out on p 139, the embryonic cloaca becomes divided by a horizontal partition, the urorectal septum, into a dorsal or rectal part and a ventral or urogenital part (Figs 146 and 147) This division begins in embryos of about 5 mm and is completed in embryos of 15 mm (less than seven weeks) With this division the cloacal membrane, which is yet intact, becomes divided into anal and urethral (urogenital) membranes The urethral membrane ruptures shortly after the completion of the division (Fig 147A and B) After the division of the cloaca the allantois and the urogenital ducts (Mullerian and Wolffian) are tributaries of the urogenital portion of the cloaca, the urogenital ducts lying close together on the dorsal surface at Muller's tubercle (Figs 147 and 149)

Even before the division of the cloaca is completed, the ventral (urogenital division) begins to show three transverse subdivisions (1) The cephalic end, from the entrance of the Mullerian ducts to the base of the allantois, is the vesico-urethral part, which early becomes enlarged (2) The middle part, beginning at the Mullerian ducts, is

the more slender pelvic part. (3) The terminal division is the phallic part, which also is somewhat expanded (Fig. 147A). The pelvic and phallic parts together are called the urogenital sinus. From these three divisions, together with surrounding mesenchyme, the bladder, the urethra, and the vaginal vestibule develop in the following manner.

By appropriate growth, the vesico-urethral part produces the bladder. The apical part lags in its expansion and becomes a slender, tubular appendix, to which is attached the allantois. It soon degen-

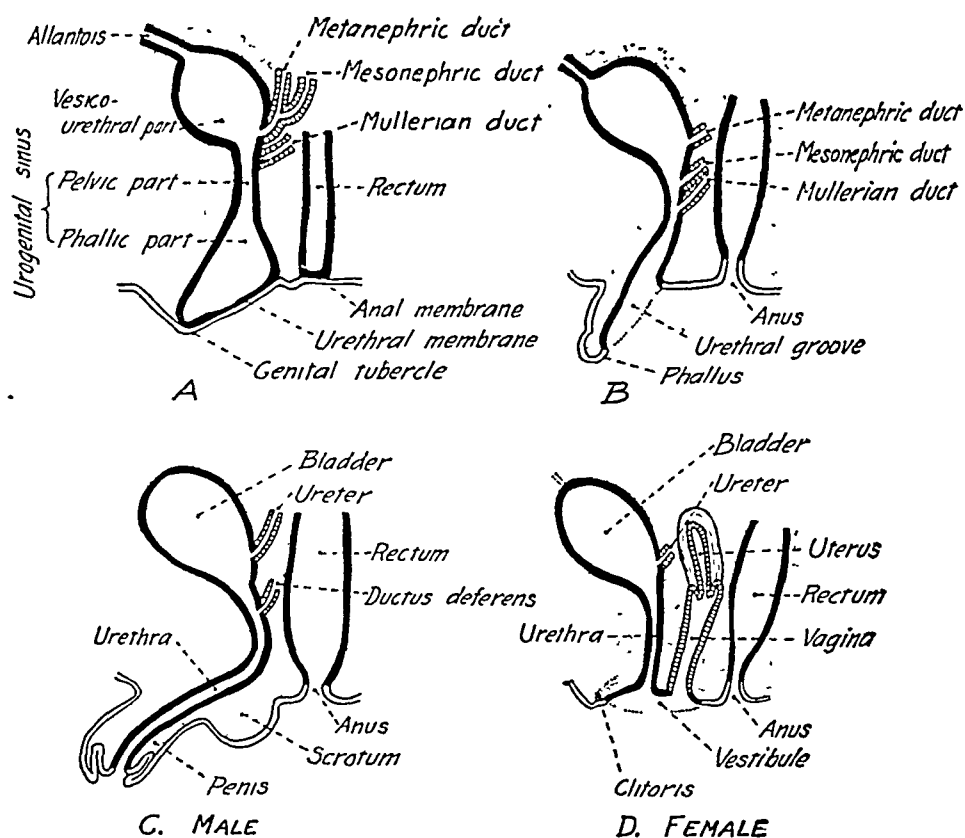


FIG. 147. Diagrams to show development of bladder, urethra, and external genitals, as seen in sagittal sections. A, early stage, when genital tubercle is low, and urethral and anal membranes are intact. B, the phallus has developed, and urethral and anal membranes have ruptured. C, the definitive male condition. D, the definitive female condition.

erates to form a fibrous cord, the *urachus* or *middle umbilical ligament*, connecting the apex of the bladder with the umbilicus. A short segment of the vesico-urethral division, just cephalad to Müller's tubercle, does not share in the expansion but remains of small diameter. The entire female urethra develops from this segment. The much longer male urethra is formed by adding to this

segment the entire urogenital sinus (pelvic and phallic parts) The male urethra thus becomes a urogenital duct, carrying both renal and genital products In the female the urogenital sinus becomes shortened to form the shallow vaginal vestibule, into which excretory and reproductive ducts open separately (Fig 147D)

In their primitive relations the ureters do not open directly into the bladder but are tributaries of the Wolffian ducts, which open into the urogenital sinus at Muller's tubercle (Figs 146C and 147A) During their further development the terminal parts of the Wolffian ducts are absorbed into the wall of the developing bladder in such a way that the ureters attain independent entrance into the bladder, whereas the Wolffian ducts (sperm ducts) retain their original entrance into the urethra a short distance below the bladder (Figs 146E and 147C) The positions of these four ducts outline the area known as the trigone of the bladder

For many years it was the general belief that the absorption of the mouths of the Wolffian ducts takes place in such a way that they contribute their mesodermal epithelium to the trigone of the bladder, which thus becomes a mesodermal area surrounded by entoderm Certain more recent studies, however, indicate that the mesodermal epithelium of the ducts degenerates in the absorption process so that the trigone, like the rest of the bladder, has entodermal epithelium ✕

D THE EXTERNAL GENITALS

The external genitals, though showing slight sexual differences almost from the beginning, have very similar origin in the two sexes, and all the parts in one sex have their exact homologues in the other

In embryos of about five weeks, at a time before the urogenital sinus has been formed by the division of the cloaca, there begins to develop a conical elevation, the genital tubercle, surrounding the part of the cloacal membrane where the urogenital opening will later develop (Fig 148A) On the caudal surface of the genital tubercle there is a median furrow, the urethral groove, bordered by two ridges, the urethral folds (Fig 148A) At the bottom of the urethral groove is the urethral membrane, inside which lies the phallic part of the urogenital sinus (Fig 147A) The urethral groove is separated from the anal pit by a transverse ridge

The genital tubercle soon assumes a cylindrical shape in both sexes and is then known as the phallus (Fig 148B and D) The phallus very early develops a bulb-like enlargement, the glans, at its tip The urethral groove extends along the caudal side of the phallus, in the male extending into the glans, in the female not quite to it This

feature, however, is variable, and sex cannot certainly be recognized in embryos under 50 mm. CR length. The phallic part of the urogenital sinus extends into the genital tubercle as a narrow cavity just inside the urethral membrane (Fig. 147A). When the urethral membrane ruptures in embryos of about 17 mm. (seven weeks), the phallic part of the sinus becomes continuous with the urethral groove, which

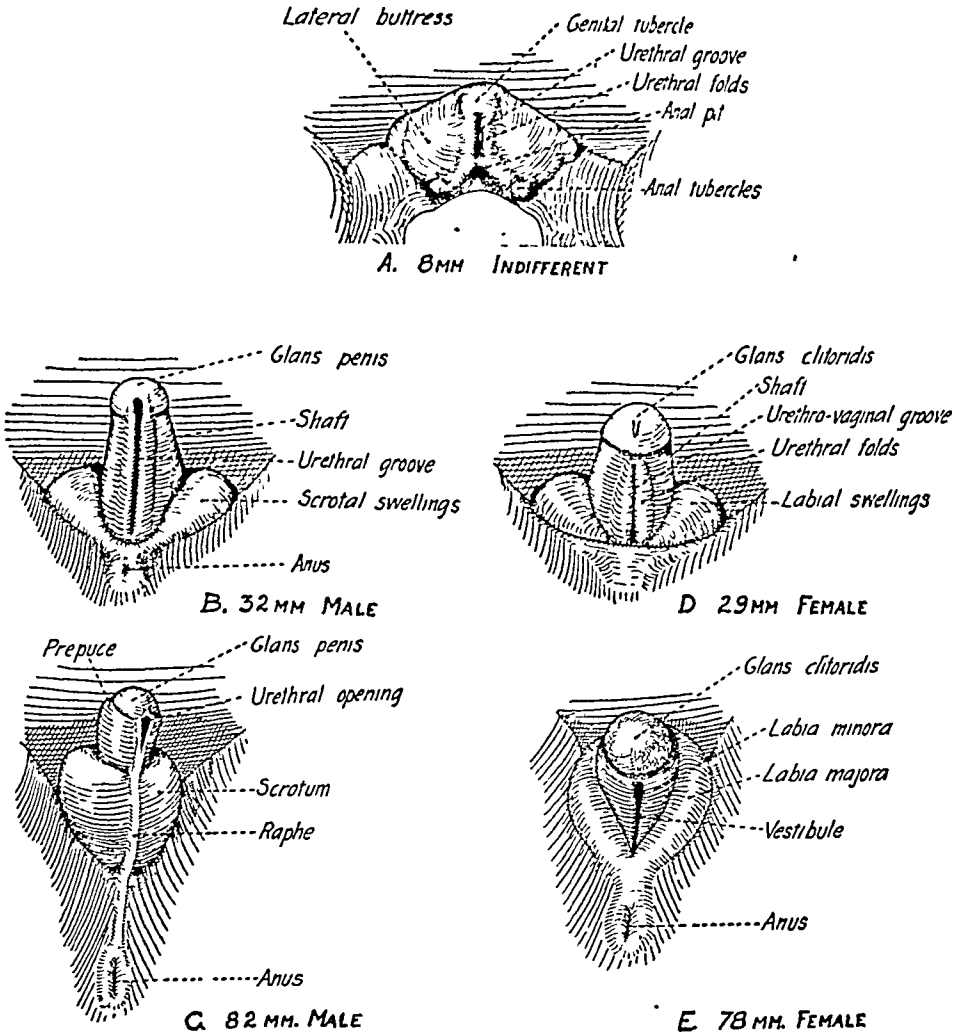


FIG. 148. The development of the external genitals. (Redrawn from photographic figures by Spaulding in *Cont. to Emb.*, Carnegie Inst., Washington.)

now communicates with the internal portion of the sinus at its basal end by the **primitive urethral opening** (Fig. 147B). At the base of the phallus, on right and left sides, a pair of ridges, the **labio-scrotal swellings**, develop very early (Fig. 148B and D). The above structures constitute the rudiments of the external genitals in both sexes.

Differentiation in the Male. In the male the phallus elongates to a

considerable extent and becomes the penis. The part of the urethra in the penis (the phallic part) is at first represented by the open urethral groove, the primitive opening of the urethra being at the base of the penis. About the middle of the second month the edges of the urethral groove begin to fuse, again enclosing the phallic part of the urethra in the penis, except at the terminal urethral opening in the end of the glans. The closure begins at the base of the penis and progresses toward the tip, being completed about the close of the third month (Figs 147C and 148C). The pelvic part of the urogenital sinus forms the part of the urethra between the base of the penis and the ejaculatory ducts (Fig 147A and C). The prepuce forms from folds which appear on the shaft at the base of the glans about the end of the third month, and by the middle of the fourth month it covers the glans.

The two scrotal swellings in the male migrate slightly caudad to the base of the penis and fuse together in the median line to form the scrotum (Fig 148C). Into the scrotal swellings there grow, through the inguinal canals, two extensions of the body cavity, the vaginal processes, lined with peritoneum (Fig 152, left side). About the eighth month the testis and epididymis descend through the inguinal canal into the scrotum (Fig 152). During this descent the testis and epididymis continue to be covered with a reflected portion of the peritoneum.

During the descent of the testis the sperm duct and the nerves and blood vessels of the organ are drawn down along with it. These structures become invested with connective tissue to form the spermatic cord. After the descent of the testis the vaginal process becomes the tunica vaginalis, with its parietal layer lining the scrotal sac and its visceral layer covering the testis and epididymis (Fig 152). After birth the vaginal process becomes separated from the peritoneal cavity by the closure of the inguinal canal.

Differentiation in the Female. In the female the labial swellings (corresponding to the scrotal swellings in the male) remain in much their primitive position and develop directly into the labia majora (Fig 148D and E). The edges of the urethral groove do not fuse to form part of the urethra, as in the male, but remain separate to become the labia minora (Fig 148E). The urogenital sinus, from the entrance of the Mullerian ducts (utero-vaginal canal) to the exterior, shortens considerably to become the vaginal vestibule, the shallow cleft into which the adult vagina and urethra open (Figs 147D and 148E). The remainder of the phallus (the cavernous portion and the glans) undergoes only slight development and becomes the clitoris,

which for a time projects freely (Fig. 148E) but soon becomes wholly covered over by other structures (Fig. 147D). The female urethra, accordingly, corresponds to only that part of the male urethra between the ejaculatory ducts and the bladder, inasmuch as it does not include any part of the urogenital sinus.

E. THE ACCESSORY REPRODUCTIVE GLANDS

The Prostate and the Paraurethral Glands. During the third month several glandular sprouts arise from the urethral epithelium around the openings of the mesonephric ducts. In the male these buds develop into the epithelium of the prostate gland, its fibrous and muscular parts coming from the surrounding mesenchyme. Some of these buds have been thought to come from the mesodermal epithelium of the trigone. But if, as now seems to be the case, the trigone too is entodermal, the entire epithelium of the prostate is entodermal. In the female these buds give rise to the paraurethral glands.

The Bulbourethral and Vestibular Glands. Early in the third month certain buds from the urogenital sinus grow into the surrounding mesenchyme, which in the male develop into the bulbourethral glands (Cowper's glands) and in the female, into the vestibular glands (Bartholin's glands).

F. THE LIGAMENTS OF THE GENITAL ORGANS

The ligaments of the genital organs are derivatives of the peritoneum, comparable to the mesenteries and omenta, but they were not treated along with the general development of the body cavities. The ligaments, like other parts of the reproductive system, have similar origins in the two sexes, though the final adult structures differ greatly.

In the Female. In the female three adult ligaments must be accounted for: the broad and round ligaments of the uterus and the ligament of the ovary.

The broad ligament develops from a portion of the mesonephros and its mesentery thus: In the region of the body where the utero-vaginal canal is giving rise to the uterus, the mesonephroi and their mesenteries connect the developing uterus with the floor and lateral walls of the pelvis (Fig. 149). As the glandular tissue of the mesonephros degenerates, there remains of the organ a fibrous sheet covered with peritoneum. This is the broad ligament which connects the uterus with the lateral walls and floor of the pelvic cavity. This ligament, together with the uterus, forms a partition separating the recto-uterine and vesico-uterine pouches of the pelvic cavity (Figs. 149 and 151).

The manner of development of the broad ligament may well be illustrated by cross sections showing two phases of the process (Fig 150) As the Mullerian ducts approach the mid plane of the body (indicated by arrows), where they fuse to form the utero-vaginal canal, the right and left members of the primitive broad ligament are thereby joined, establishing the recto-uterine and vesico-uterine pouches While the uterus is increasing in bulk, the mesonephros are

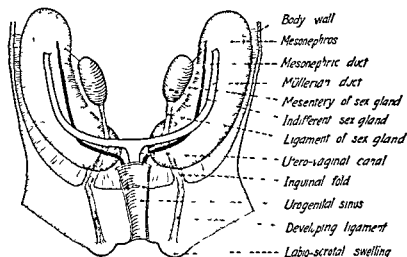


FIG 149 Diagrammatic representation of the indifferent stage of the reproductive organs as seen in a ventral dissection This figure and the two following are designed especially to show the development of the ligaments of the internal genitals The metanephros is omitted

degenerating to form the broad ligament When the broad ligament thus becomes established, the ovary is attached to its dorsal surface by the short **mesovarium**, this position of the ovary being due to its earlier attachment to the mesial surface of the mesonephros By the same process the uterine tubes come to lie in the superior margin of the broad ligament (the **mesosalpinx**) while the epoophoron (persisting tubules of the mesonephros) is embedded in the ligament (Figs 149 and 151)

The ligament of the ovary connecting it with the fundus of the uterus is derived from the caudal portion of the genital ridge, which does not take part in the formation of the sex gland (Fig 149) Inasmuch as the genital ridge is attached to the mesonephros on a mesentery-like structure, the ligament derived from it is also enclosed in a fold of the dorsal surface of the broad ligament (Figs 149, 150, and 151)

The round ligaments of the uterus, which are also embedded in the tissue of the broad ligament, are derived from two separate segments

which join end to end. The internal segment is the **gubernacular cord**, which forms in the inguinal fold between the mesonephros and the pelvic floor (Fig. 149). The gubernacular cord extends from the mesonephros into the inguinal canal. The external segment is the **labial ligament**, which extends from the inguinal canal into the

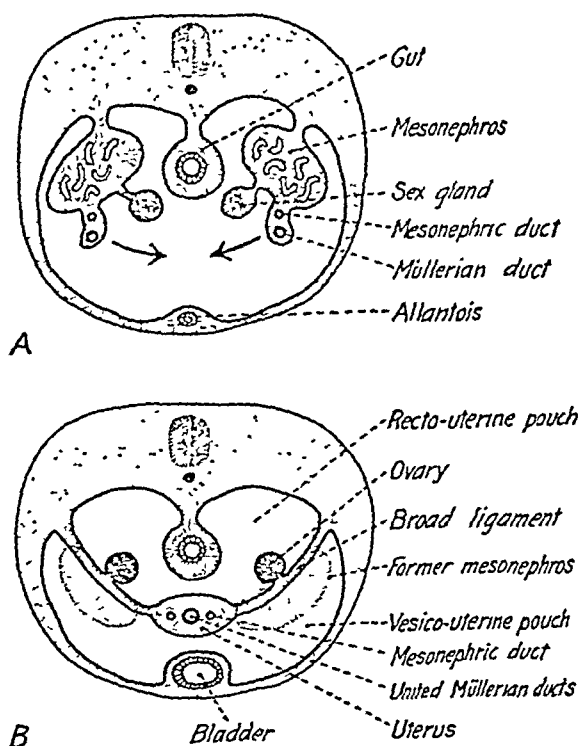


FIG. 150. Diagrams of cross-sections to show chiefly the formation of the broad ligament of the uterus. *A*, section through indifferent stage at level of gonads. Arrows show direction of growth by which the two Müllerian ducts unite to form the utero-vaginal canal. *B*, section through an older embryo at the level of the descended ovaries. (Adapted from Eycleshymer, in *Morris' Anatomy*, P. Blakiston's Son and Co., Philadelphia.)

labial swellings. As the mesonephros degenerates and the uterus grows, the inner end (the gubernacular cord) becomes embedded in the mesenchyme of the expanding uterine wall, and the outer end (the labial ligament) is attached in the skin of the labia majora, thus attaining the adult relations (Fig. 151).

In the Male. In the male the embryonic structures which correspond to the broad ligament of the uterus become fused to the dorsal wall of the bladder and do not develop into any recognizable adult structure. The gubernaculum testis is formed by the end-to-end union of three segments corresponding to the three elements in the female, namely, the ligament of the testis, the gubernacular cord, and the

scrotal ligament (Fig 149) The three join to form a continuous cord, the gubernaculum testis, extending from the caudal end of the testis through the inguinal canal to the bottom of the scrotum (Figs 152

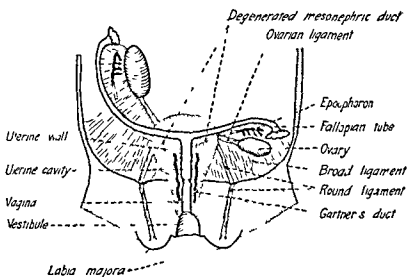


FIG 151 Diagrammatic representation of the female reproductive organs, showing the derivatives of the various structures illustrated in Fig 149 On the left side of the figure, the ovary and associated structures are shown in their primitive position on the right, in the position assumed after their descent

The degenerated parts of the mesonephric ducts are shown in dotted lines

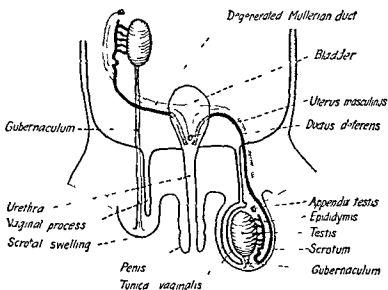


FIG 152 Diagrammatic representation of the male reproductive organs, showing the derivatives of the various parts illustrated in Fig 149 On the left side of the drawing, the testis and associated structures are shown in their primitive position on the right in the position assumed after their descent The degenerated parts of the Mullerian ducts are shown in dotted lines

and 153). The reason why the two parts of the cord unite into one continuous gubernacular cord in the male, instead of forming two separate ligaments as in the female, is that the development of the utero-vaginal canal is so slight that the cord does not become connected to it as it does in the female.

The gubernaculum is, in part at least, responsible for the descent of the testis. During the growth of the fetus the gubernaculum not only fails to keep pace with the rest of the body in growth but also actually becomes shorter. The result is that the testis, attached by it to the bottom of the scrotum, gradually descends until about the eighth month it reaches the scrotal sac, after which the gubernaculum degenerates almost completely (Fig. 152, right side).

G. THE DETERMINATION OF SEX AND THE DEVELOPMENT OF SEXUALITY

It has been seen in the preceding pages that during the development of the reproductive organs all parts (glands, ducts, external genitals, and ligaments) pass through an indifferent stage in which there appears to be the possibility of their developing into those of either sex. The question naturally arises whether the individual in these early stages is really an indifferent or sexless being or only seems so. Has the sex of the individual been determined before the transformation of the indifferent rudiments of the sexual organs, or is this transformation the actual determination of sex?

On the basis of the chromosome theory of *sex determination*, the sex of the individual is determined at the moment of fertilization, according to whether the act is accomplished by a male-producing or a female-producing sperm. It is safe to say that the great majority of careful students of the subject consider this to be the method. The evidence presented in Chapter II is but a small part of a large body of observation upon animals of various groups which indicates that sex is determined in that way, and that the difference between male and female individuals extends to the chromosomes of every cell of the body. Difficulty exists in proving this with respect to the cells of the various organs of the adult body because the cells are small. At the time they are undergoing maturation, however, these chromosome counts can be made, as they can in the somatic cells of young embryos of some animals; in all these cases the sexual difference exists.

Sex in all probability is determined at the time of fertilization (p. 13). This is by no means the whole story, however, and it is quite evident that the development of sexuality or of sexual differ-

ences, both primary and secondary, takes place at later times and is not wholly completed until well along in life. Moreover it is increasingly well known that in the development of sexuality the hormones secreted by the ovaries and testes have an influence upon the development of both primary and secondary sex characters. The modified development which follows the removal of the gonads from young mammals and birds has long been recognized as indicating such

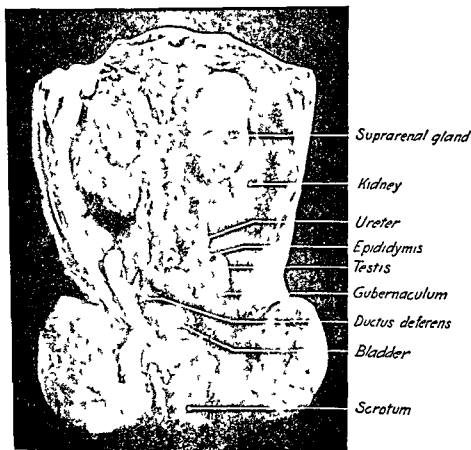


FIG 153 Dissection showing urogenital organs in fetus of about 200 mm CR length (less than 6 months). Photograph about natural size

an influence. It was not until more recent years, however, that the influence of sex hormones upon development, both pre- and postnatal, has received much experimental study.

One of the very significant contributions upon this subject is due to study of the free martin in cattle. It has been known for many years that, when twin calves are of opposite sexes, the female twin is nearly always infertile, though the male is normal. The infertile female is known as a free martin. By a careful study of twin fetuses, it has been learned that quite early in embryonic life the development of

the sex organs of the free martin shows departure from the female type, with both internal and external genitals tending strongly toward the male type, though there is much variation in the exact pattern. It was clearly shown that the animal is really a female to start with and that, though distorted, it is not transformed into a male.

Such modification of female type was found only when there was a vascular anastomosis between the two placentas, allowing exchange of fetal blood. The postulated explanation, amply supported by recent experimental work, attributed the faulty female development to hormones produced by the testis of the male twin and reaching the female through the blood. The reason why the female twin, rather than the male, is affected seems to lie in the fact that the differentiation of the testis begins earlier than that of the ovary and therefore the testis sooner becomes capable of producing the sex hormone. It should be remarked that, for reasons not clearly understood, nothing comparable to the free martin has been observed in human twins, nor indeed in most other species.

Since these early observations upon the free martin (1917), much experimental work has been carried on, which has given convincing evidence of the great importance of the hormones produced by the early sex glands in guiding the development of the indifferent sex organs. The general opinion is that the early differentiation of the gonad is determined by the chromosomes, and that this early differentiation soon leads to the production of male and female hormones which guide the later differentiation in the transformation of the indifferent (bipotential) primordia into those of one sex. In the beginning, however, it is the genes that seem to determine the nature of the hormone, whether male or female, that is produced.

Though the preceding paragraphs give certain important facts about sex determination and the development of sexuality, the matter presented is scarcely enough to serve as a beginning for a discussion of the subject. It is not possible here to give even a brief outline of the mass of fact and theory bearing upon the subject and gathered from many groups of animals. Many of the observed facts are seemingly contradictory, and it is not yet possible to bring all together under one consistent hypothesis. Among the important topics which might be discussed are: intersexuality and hermaphroditism (see p. 227), parthenogenesis and sex determination, environment and sex determination, chromosomes and sex determination, hormones and sex determination, differential metabolism and sex determination, and sex reversal.

H ANOMALIES

Excretory Organs Rarely, both kidneys are absent, more often they are seriously defective, so that the infant dies shortly after birth. Absence of one kidney or the fusion of both kidneys into one mass may occur. Sometimes the kidneys fail to migrate from the pelvis into the lumbar region, and sometimes they migrate too far. The pelvices and ureters are subject to variation. The lobulated form of the embryonic kidney sometimes persists. A frequent anomaly is cystic kidney, in which some of the secreting tubules fail to make connection with the collecting tubules and so develop into cysts without outlets.

The urinary bladder in rare cases is wholly wanting. The bladder is often involved in non-closure of the ventral body wall. Persistence of the allantois between the bladder and the umbilicus produces a urinary fistula. Failure of the cloaca properly to divide into rectum and urogenital sinus results in various serious malformations.

Reproductive Organs The reproductive organs are subject to frequent anomalies, both external and internal, which arise from failure of the indifferent stage to develop properly into the male or female type.

Absence of one or both testes is rare. More frequently the descent of the testes into the scrotum does not occur, a condition known as **cryptorchidism**, in which case the testes usually fail to develop fully and the male secondary sexual characters usually develop imperfectly.

Both ovaries are rarely absent. Malformation due to incomplete descent occurs, or the ovaries may descend through the inguinal canals into the labia majora. Both ovaries and testes are subject to congenital cysts and teratoid tumors.

The fusion of the two Mullerian ducts may be incomplete or fail entirely, resulting in a uterus and vagina double to varying extents. Infantile uterus due to non-development occurs. The penis sometimes fails of complete development, in that the urethral groove remains open as a furrow along the ventral surface of the organ, a condition known as **hypospadias**. More rarely there is a similar defect on the dorsal surface, its explanation being less obvious.

Hermaphroditism is the presence of both male and female characters in the same individual. Two kinds may be recognized: (1) **true hermaphroditism**, in which both ovarian and testicular tissue are present, and (2) **false hermaphroditism**, where the sex glands are of one sex, but the other sexual characters somewhat resemble those of the opposite sex.

True hermaphroditism is the rule in some groups of invertebrates, but self-fertilization does not occur. In vertebrates the condition

occurs rarely as an anomaly. In man a few cases have been described in which both ovarian tissue and testicular tissue were present in one individual, but in none of these anomalies were both ova and sperms actually produced. The external and internal genital organs were variously and imperfectly developed, and secondary sexual characters inclined in some cases toward the female and in others toward the male. True hermaphroditism in man and other vertebrates presumably comes about by persistence of both the first (male) and the second (female) proliferation of cells from the germinal epithelium, so that an ovo-testis is produced, or an ovary occurs on one side and a testis on the other.

False hermaphroditism is much more common. The more frequent type is that of male individuals who have external genitals and secondary sexual characters approaching in varying degrees those of the female. Less frequent is the female type, where ovaries are present, but in other respects male characteristics predominate. Unbalanced hormone production, resulting in faulty differentiation of the indifferent sex primordia, probably lies behind the condition.

In connection with these extreme cases of faulty development of sex organs, it is of interest to note the more frequent cases of masculine women and feminine men, in whom the physical and mental characters that go to make up what we call maleness or femaleness have become associated, to greater or less extent, with the wrong sex. In this group lie various forms of sexual perversion, in which the development of sexuality has not followed the usual course, though the sex organs themselves are normally formed and functional.

CHAPTER XVIII

THE NERVOUS SYSTEM

The nervous system is one of the earliest systems of organs to begin its development and is among the last to complete it. Its first primordium, the neural groove, appears before the close of the third week, at the very beginning of embryo formation. It does not, however, spring quickly into a state of efficient function, as does the circulatory system, but rather pursues a steady course of progress, not only during prenatal life but also during the years of childhood and youth. It should also be remembered in this connection that the development of the nervous system goes hand in hand with that of the sense organs, the muscles, and other parts, through which the activities of the system are manifested.

There are many evidences of nervous activity during prenatal life. Long before birth the nervous system has developed so far as to coordinate certain muscular movements of the fetus, so that they are more or less purposeful and may be produced in response to external stimuli. The fetus has alternating periods of activity and rest, possibly sleep. It changes its position at times, as if assuming a more comfortable attitude. Hiccough is not uncommon in unborn babes, and cases are on record of fetuses that have clearly indulged in the habit of sucking the thumb for some time before birth. At the time of birth the nervous system has developed to such a state that it is able to coordinate the activities necessary to the life of the child, though the great development of muscular control and intellectual power which characterizes the adult human being still remains to be accomplished.

A THE ORIGIN OF THE NERVOUS SYSTEM

The nervous system is derived from ectoderm through two primordia, the neural tube and the neural crest.

The Neural Tube. The neural tube begins as the neural plate, a thickened band of ectoderm along the mid line of the embryonic disc, extending from the primitive node to the anterior end of the embryonic area. The central line of this plate becomes depressed to form the neural groove, which is bounded by two elevated ridges, the neural folds. The neural groove is already present in the *Spina* embryo

(1.54 mm.), when the embryo is just beginning to form (Fig. 18, p. 42). The groove deepens and the folds approach each other and fuse, thus forming the neural tube. The closure has already begun in embryos of about 2 mm. The external appearance of this process is shown in Figs. 19 and 20, p. 43. The formation of the neural tube as it is seen in cross-section is shown in the four drawings of Fig. 154. The neural tube develops into the central nervous system, the anterior end becoming enlarged and highly specialized to form the brain, while the rest of it remains of smaller diameter and forms the spinal cord.

The Neural Crest. Just before the neural groove closes to form the

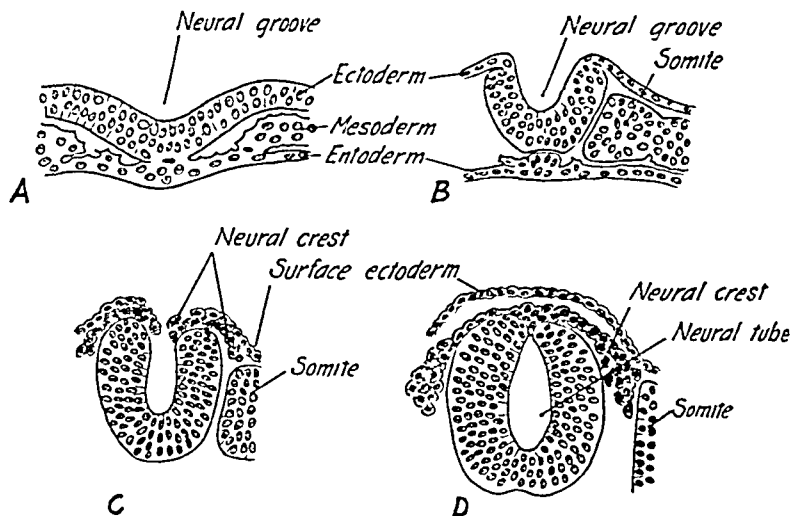


FIG. 154. Cross-section to show the mode of formation of the neural tube and the neural crest. (Redrawn from Hardesty in *Morris' Anatomy*, P. Blakiston's Son and Co., Philadelphia.)

neural tube, there appears along each side, in the angle where the neural plate meets the surface ectoderm, a band of cells, the **neural crest** or **ganglion crest** (Fig. 154). The neural crest apparently is formed by separation of cells from the dorsal edge of the neural tube. At first the neural crests are continuous bands of tissue lying in the angles between the neural tube, the surface ectoderm, and the somites (Figs. 53, p. 82, and 154). Soon, however, the parts of the crest opposite the somites enlarge to form the **spinal ganglia**, while the intermediate parts disappear. The neural crest in the head region contributes to the formation of the **sensory cranial ganglia**.

B. HISTOGENESIS OF NERVOUS TISSUES

The Neural Tube. The cells of the neural tube eventually become differentiated into two distinct types, **nerve cells** and **neuroglia cells**,

in the following manner. The wall of the neural tube at first consists of a single layer of columnar cells but, as the cells multiply by mitotic division, the nuclei assume different levels and form a broad band (Fig 155). At the same time the cell outlines become indistinct, indeed, it is generally stated that they form a syncytium as shown in Fig 155. Some recent studies, however, indicate that more probably they remain separate, the individual cells being very long and slender and oriented radially from the cavity of the neural tube. By this

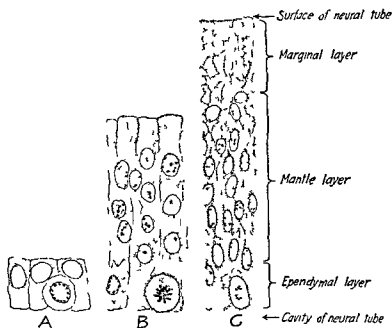


FIG 155 Three early stages in the formation of the neural tube, showing the development of the single layer of columnar cells into the three layers A, from rabbit just before closure of the tube B, from 5-mm pig C from 10 mm pig (Redrawn from Hardesty in *Am Jour Anat*)

time three layers or zones are evident (1) the ependymal layer, a single zone of columnar cells bounding the neural canal, (2) the mantle layer, a middle zone with many nuclei, (3) the marginal layer, an outer zone composed of cytoplasmic strands without nuclei (Fig 155C). The cells of the mantle layer are produced by multiplication of the cells of the ependymal layer, and they later increase in number by cell division in the mantle layer itself. The multiplication of cells in the nervous system takes place very rapidly during the early stages of development. It is by multiplication of these cells that the very many cells of the nervous system are produced. During the later stages of development the increase in size of the brain and

spinal cord is due to the growth of these cells and the production of nerve fibers and neuroglia fibers.

The cells of the mantle layer are indifferent cells, at first all of the same kind, but soon they differentiate into two types: (1) neuroblasts (primitive nerve cells), and (2) spongioblasts (primitive neuroglia cells). In the early differentiation of these types, the neuroblasts become somewhat pear-shaped cells with large nuclei. From the narrow end of each neuroblast a cytoplasmic process, the axone, grows out and the dendrites arise in a similar manner from other parts

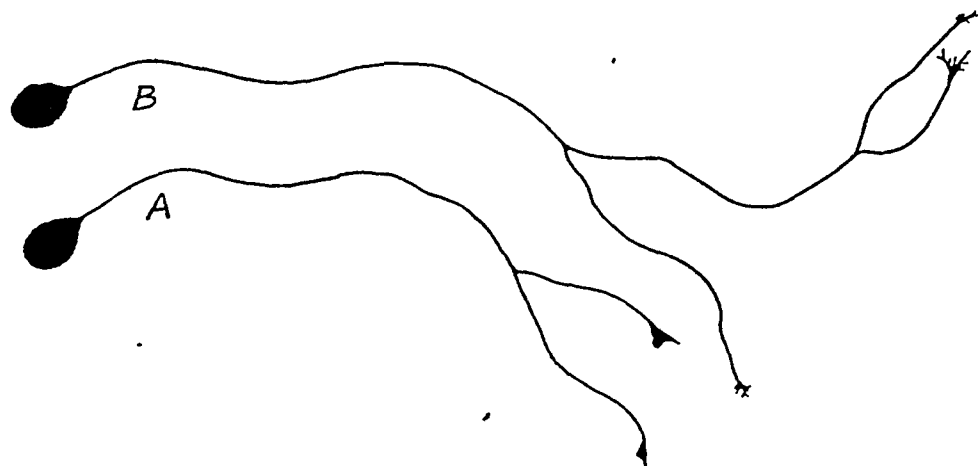


FIG. 156. Outline figure showing a nerve fiber growing from a nerve cell of the neural tube of a frog embryo. The growth is taking place in clotted lymph on a microscopic slide. *B* shows the same cells as *A*, but after an interval of 4½ hours. (Redrawn from Harrison in *Jour. Exp. Zool.*)

of the cell. Thus nerve fibers develop as outgrowths from the cytoplasm of neuroblasts, a single neuroblast in this manner giving rise to a neurone.

The actual growth of axones from neuroblasts was first observed in cells from the neural tubes of frog embryos in clotted lymph on a glass slide (Fig. 156). It has more recently been studied extensively in the transparent web of the tail of living frog larvae. Growth of the fibers is accomplished by terminal growth cones of amoeboid form (Fig. 156). As a cone advances it spins a fiber behind it. The earliest fibers of a nerve advance independently through the mesenchyme, whereas the later fibers glide along the earlier ones. It is not known what guides the first fibers.

Those cells of the mantle layer which do not become neuroblasts become spongioblasts, which develop into neuroglia tissue. In the development of neuroglia the cytoplasmic processes of the neuroglia cells become very slender, and neuroglia fibers develop in them or

closely associated with them. They thus form a delicate network connecting the neuroglia cells and enveloping and supporting the developing nerve cells and their processes. The ependymal cells, whose nuclei lie near the central canal, have long processes extending outward through both mantle and marginal layers. These processes become part of the neuroglia tissue, while the cell bodies persist as the ependymal cells of adult life. The supporting tissue of the central nervous system includes also some connective tissue of mesodermal origin, derived from mesenchyme which invades the neural canal, chiefly along with developing blood vessels. The exact amount of this tissue has not been determined, but it is probably small.

The Neural Crest The histological differentiation of the neural crest resembles in general that of the neural tube. It develops first into a mass of indifferent cells, which differentiate into *neuroblasts* and *supporting cells*. The development of the neuroblasts, which become the ganglion cells, is essentially the same as in the neural tube. The supporting cells, instead of forming a network of neuroglia cells and fibers, develop into the flattened capsule cells which surround the individual ganglion cells. Some of the primitive supporting cells migrate from the ganglia along the axones of the peripheral nerves and develop into the neurilemma (sheath of Schwann) surrounding the nerve fiber. It is possible that the neurilemma of some fibers may develop from cells which migrate from the spinal cord along the ventral root of the spinal nerves.

The Formation of the Myelin Sheath In frog larvae it has been observed that myelin is formed, apparently by an interaction between primitive sheath cells and nerve fibers. Each myelin segment is under the influence of one sheath cell. Myelin forms first adjacent to the nucleus and spreads toward the ends of the segment. It is not known why myelin forms about some fibers and not about others.

C THE DEVELOPMENT OF THE SPINAL CORD AND SPINAL NERVES

Development of the Spinal Cord It will be convenient to take up the development of the spinal cord before that of the brain because the cord is the simpler of the two. The neural tube in the region of the spinal cord remains of about uniform diameter throughout its length, except for two slight swellings, the cervical enlargement opposite the brachial plexus and the lumbar enlargement opposite the lumbosacral plexus.

During the differentiation of the ependymal, mantle, and marginal layers of the early spinal cord, the mantle layer develops greatly on

the two sides of the neural tube but not at all dorsally and ventrally, thus forming the thin roof plate and floor plate (Fig. 157). One result of this unequal thickening of the wall is that the neural canal, originally a large cavity (Fig. 154D), becomes compressed laterally into a narrow slit which soon becomes somewhat diamond-shaped by the formation of two lateral angles, known as the sulcus limitans (Fig. 157A). The sulcus limitans marks the division between the dorsal or alar plate (sensory) and ventral or basal plate (motor) of the tube (Fig. 157A).

At about nine weeks the dorsal part of the central canal becomes obliterated by the fusion of its sides (Fig. 157B and C). Along the line of fusion the ependymal cells form the dorsal median septum.

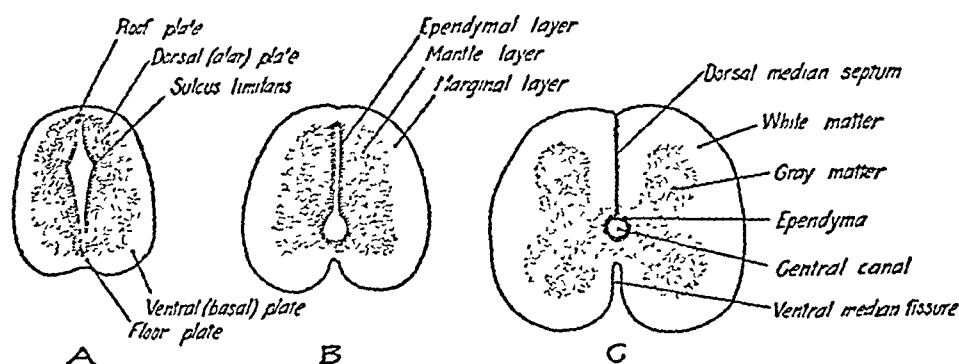


FIG. 157. Diagrams of cross-sections through three stages of the spinal cord, to show the development of the gray and white matter and the mode of formation of the central canal.

The remainder of the canal persists as the central canal of the spinal cord. The central canal is separated by the floor plate from the ventral median fissure, a longitudinal groove on the outside of the developing cord (Fig. 157B and C).

Development of the Gray Matter of the Cord. The mantle layer develops directly into the gray matter of the spinal cord, its neuroblasts becoming the neurones of this region. The ventral or anterior gray column arises as a thickening of the ventral plate in embryos of 10–15 mm. The dorsal or posterior gray column appears in embryos of about 20 mm. as a thickening of the dorsal plate (Fig. 157C).

Development of the White Matter of the Cord. The white matter of the spinal cord develops in the marginal layer of the neural tube. This layer is, at the first, composed mainly of a network of processes from neuroglia and ependymal cells (Fig. 155C). Into this network grow axones from neurones developing in the gray matter. When these axones attain their myelin sheaths, the tissue takes on the glistening appearance characteristic of the white matter of the nervous system.

These fibers grow from neuroblasts in three different locations (1) the spinal ganglia, (2) the gray matter of the spinal cord, and (3) the gray matter of the brain. They become organized into the various bundles or columns of the spinal cord according to the place of their origin.

Development of the Spinal Nerves Each spinal nerve includes fibers of the four functional nerve components: somatic motor (somatic efferent), visceral motor, somatic sensory (somatic afferent), and visceral sensory (Fig 158). These fibers grow from neuroblasts in three locations: (1) In the ventral and lateral gray matter of the spinal cord lie the neuroblasts from which grow the somatic and visceral motor axones which make up the ventral roots of spinal

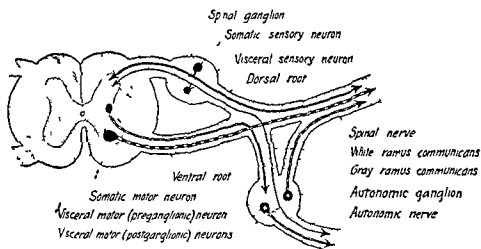


Fig 158 Diagram showing the growth of the different functional groups of nerve fibers in the spinal nerves and the autonomic nervous system. The arrow heads show the direction in which the fibers grow.

nerves (Fig 158). The beginnings of the ventral roots are seen in embryos of about 4 mm (less than five weeks). (2) In the primordia of the ganglia of the sympathetic trunks lie the neuroblasts from which grow the axones of those visceral motor fibers which reach the spinal nerves through the gray rami communicantes. (3) In the primordia of the spinal ganglia lie the neuroblasts from which grow both somatic and visceral sensory fibers of the dorsal roots. Each of these neuroblasts develops at first as a bipolar cell, the axone growing into the dorsal gray column of the spinal cord, and the long dendrite to the peripheral sense organs. Soon, however, the two processes fuse at their origins and both take on the structure of axones, the result being, in effect, unipolar cells with single, T-shaped axones (Fig 158).

The somatic sensory fibers grow out to the sensory terminations

in the skin and the somatic motor fibers to the striated musculature of the body and limbs (Fig. 158). In certain regions of the body, notably those opposite the limb buds, there is intermingling of the somatic fibers of adjacent spinal nerves, which results in the formation of the brachial and lumbo-sacral plexuses (Fig. 169).

The visceral fibers, both sensory and motor, branch off from the spinal nerves as the white rami communicantes. Through these rami, the visceral fibers reach the autonomic system, and in it are distributed to the sensory and motor structures of the viscera (Fig. 158). (See p. 253.)

Up to the fourth month the spinal cord occupies the full length of the spinal canal, terminating at the last sacral segment. After that time the vertebral column grows in length faster than does the spinal cord, a fact which causes the terminal end of the cord to withdraw up the canal as far as the second lumbar vertebra. Its surrounding membrane (pia mater), however, remains connected to the coccyx and becomes drawn out into the slender *filum terminale*. As another result of this process the spinal nerves, which originally extend out at about right angles from the cord, come to run highly oblique courses from the cord to the vertebral foramina. This condition is especially pronounced in the posterior region, where, beyond the end of the spinal cord, the spinal nerves of the lumbar, sacral, and coccygeal regions course almost directly caudad along with the *filum terminale* to form the *cauda equina*.

D. THE DEVELOPMENT OF THE BRAIN AND CRANIAL NERVES

The Five Divisions of the Brain

As already pointed out, the brain develops from the enlarged anterior end of the neural tube. This enlargement, however, is not uniform, and in embryos of about 2.5 mm. (four weeks) three regions of greater diameter, the three primary brain vesicles, *prosencephalon*, *mesencephalon*, and *rhombencephalon*, develop.

Very soon thereafter (about 3 mm.) the *prosencephalon* becomes divided into the *telencephalon* and *diencephalon* (Fig. 161), and a little later (7 mm.) the *rhombencephalon* becomes similarly divided into the *metencephalon* and *myelencephalon* (Fig. 162). The *mesencephalon* does not become subdivided. The five divisions of the embryonic brain thus produced are: (1) *telencephalon*, (2) *diencephalon*, (3) *mesencephalon*, (4) *metencephalon*, and (5) *myelencephalon* (Fig. 159). From these five divisions develop the more

complicated structures of the adult brain, where the five divisions, though greatly obscured, can still be recognized (Figs 160 and 166). The cavity of the neural tube becomes much enlarged in some divisions of the brain, the resulting cavities being the ventricles of the brain (Fig 159)

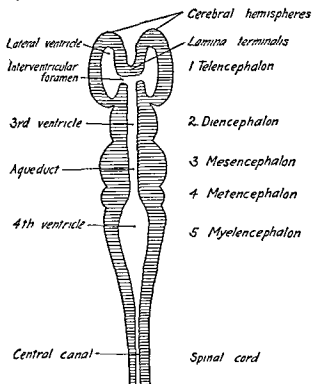


Fig 159 The plan of the early embryonic brain showing the five divisions and the primitive ventricles

The Flexures of the Neural Tube

During the early development of the brain three decided flexures or bends are formed (1) the cephalic flexure in the region of the mid brain (mesencephalon), in which the anterior end of the brain bends abruptly ventrad (Fig 161), (2) the pontine flexure in the region of the metencephalon, a sharp bend in the opposite direction to the cephalic flexure, and (3) the cervical flexure in the region of the myelencephalon, in the opposite direction to the pontine flexure (Figs 162 and 164). The cephalic and cervical flexures correspond to two bends in the body of the embryo, but the pontine flexure is confined to the neural tube and is not evident externally (Fig 24, p 46). During later development the pontine flexure disappears and the cervical flexure nearly so, the cephalic flexure persists in a somewhat reduced degree (Figs 165 and 166).

The Wall of the Neural Tube

For an understanding of the development of the brain it should be remembered that in early embryonic stages the neural tube in the brain region has the same essential structure as in the region of the spinal cord, namely, thin roof plate and floor plate with thicker side walls divided by the sulcus limitans into dorsal and ventral plates (Fig. 167). This difference, however, must be noted: the floor plate and the ventral plate do not extend forward to the extreme end of the neural tube, both being wanting in the telencephalon and the diencephalon. The ventral part of the brain in these divisions is, therefore, formed by the mid-ventral fusion of right and left dorsal plates. The floor plate is wanting also in the mesencephalon, where the two ventral plates unite in the mid line. In the early brain, as in the spinal cord, the ependymal, mantle, and marginal layers are formed. Beside the posterior end of the early brain lie a number of ganglionic masses derived in the main from the neural crest and corresponding to the spinal ganglia.

Development of the Five Divisions of the Brain

The conspicuous features which distinguish the brain from the spinal cord are produced mainly in connection with two items of development: (1) great increase of gray matter in the development of the cortex, and (2) great increase of white matter. The great mass of white matter is composed of fibers for the necessary connections between different parts of the gray matter. This great increase in gray and white matter is most marked in the cerebral hemispheres (outgrowths from the telencephalon) and in the cerebellum (a development of the metencephalon). Figures 161 to 165 show the general development of the external form of the brain up to six months. The development of each of the five divisions will now be described.

1. Development of the Myelencephalon. The myelencephalon develops into the *medulla oblongata* (Fig. 166). Both in development and in adult structure this part of the brain is intermediate between the spinal cord and the higher parts of the brain. At its posterior end it closely resembles the spinal cord both in structure and in mode of development, but more anteriorly the structure changes somewhat. In the myelencephalon the thin roof plate becomes very wide, allowing the dorsal edges of the side walls to separate until the ventral and dorsal plates come to form the floor of the organ, rather than the sides as they do in the spinal cord (Figs. 163 and 167). The cavity of the

neural tube is thus expanded into a broad, shallow space, the posterior part of the fourth ventricle

Into the thin roof plate, known as the posterior velum, a vascular network grows, which dips into the fourth ventricle to form the

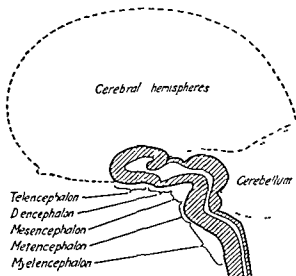


FIG 160 Diagram to show how the form of the adult brain is produced from the embryonic brain by great growth of the cerebral hemispheres and the cerebellum. The embryonic brain is shaded, the adult outline is shown in broken lines.

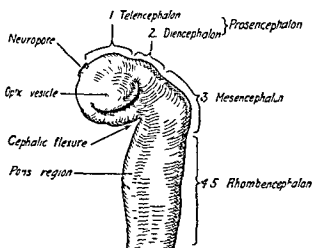


FIG 161 Lateral view of brain of human embryo 32 mm long (about 4½ weeks) (After His)

choroid plexus of the fourth ventricle. In the floor of the fourth ventricle there occur certain migrations of neuroblasts from the mantle layer into the marginal layer, for example, in the formation

of the olivary bodies, the general result being that gray and white matter are somewhat intermingled and do not have the simple arrangement which prevails in the spinal cord. The growth of the fibers in the white matter takes place in such a way that there are important crossings of fiber tracts, which are in contrast to the uniformity of the white tracts in the cord.

The cranial nerves from the sixth to the twelfth connect with the

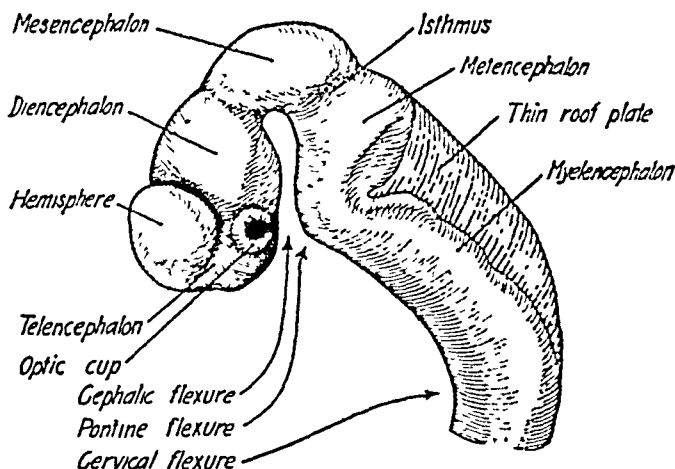


FIG. 162. Lateral view of brain of human embryo 6.9 mm. long (more than 5 weeks). (Redrawn from Kollmann's *Handatlas*.)

myelencephalon. The motor fibers of these nerves arise from neuroblasts in the ventral plate, where the motor nuclei of these nerves develop in a region corresponding to the ventral gray column of the spinal cord. Their sensory fibers arise from neuroblasts in the adjacent ganglia, whence they grow into the dorsal plate, a region corresponding to the dorsal gray column of the spinal cord (Fig. 167). The development of the individual nerves will be treated in a later section.

2. Development of the Metencephalon. From the metencephalon the cerebellum and the pons develop (Fig. 166). In this division of the brain the roof plate again becomes narrow. This condition allows the two dorsal plates to come together in the mid line in such a manner as to form a transverse ridge across the dorsal side of the neural canal. This ridge is the rudiment of the cerebellum (Figs. 162 and 163). In this ridge two swellings form near the mid line, the rudiments of the vermis, and two in a more lateral position, the rudiments of the cerebellar hemispheres. These rudiments grow greatly in volume, and at the same time their surfaces become folded to form the convolutions of the cerebellum (Figs. 164, 165, and 166).

The cortex is formed by the migration of cells from the mantle

layer into the outer or marginal layer. The axones from neuroblasts in this cortical layer grow toward the central canal (ventricle) instead of outward as they do in the spinal cord. In this manner is produced an arrangement with gray matter on the outside and white matter within it, just the reverse of the condition in the spinal cord. The dentate nucleus and other nuclei in the cerebellum are formed from certain groups of neuroblasts of the mantle layer which do not migrate into the cortex. The dorsal wall of the neural tube just in front of the cerebellum remains thin and becomes the anterior medullary velum (Fig 166).

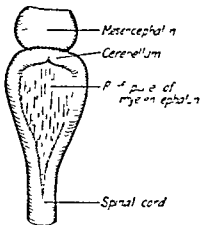


FIG 163 Dorsal view of posterior end of embryonic brain. Somewhat diagrammatic.

The pons develops in the ventral part of the metencephalon, but its nuclei seemingly are derived from the dorsal rather than the ventral plates (Figs 165 and 166). The part of the neural canal in the metencephalon becomes part of the fourth ventricle. The fifth cranial nerve arises from the pons.

3. **Development of the Mesencephalon.** In early stages of development, while the cephalic flexure is pronounced, the mesencephalon is a very prominent part of the brain (Fig 164), but during later development it grows relatively little, so that in the adult it forms only a small part of the brain that is almost wholly concealed by the cerebellum and the cerebral hemispheres (Fig 166). In the dorsal plates of the mesencephalon develop the superior and inferior colliculi (the corpora quadrigemina) and probably the red nuclei. In the ventral plates develop the nuclei of the third and fourth cranial nerves. Through the marginal zone of the mesencephalon pass the fibers of the cerebral peduncles. The neural canal in this segment becomes constricted into the narrow cerebral aqueduct (Fig 166).

4. **Development of the Diencephalon.** The diencephalon, like the mesencephalon, is a division of the brain, which, though it gives rise to several structures of considerable importance, does not attain any great size in the adult (Fig 160). The lateral walls of the diencephalon become thickened to a considerable degree, compressing the neural canal to the form of a narrow vertical slit, the third ventricle (Figs 159 and 166).

The roof plate of the diencephalon at its posterior end evaginates to form the epiphysis or pineal body (Fig 166). Its greater part

of the olivary bodies, the general result being that gray and white matter are somewhat intermingled and do not have the simple arrangement which prevails in the spinal cord. The growth of the fibers in the white matter takes place in such a way that there are important crossings of fiber tracts, which are in contrast to the uniformity of the white tracts in the cord.

The cranial nerves from the sixth to the twelfth connect with the

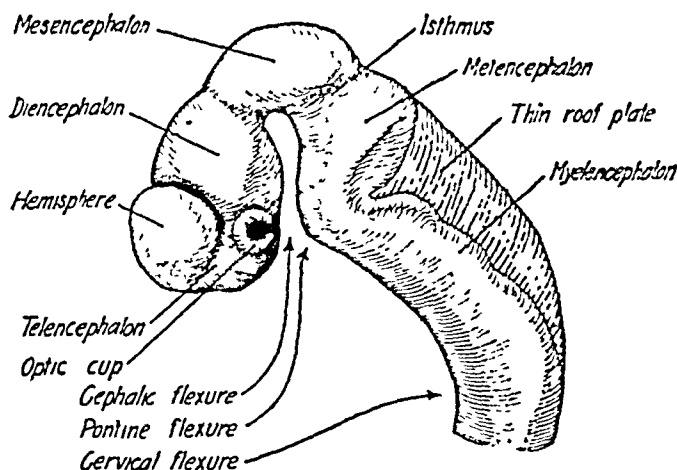


FIG. 162. Lateral view of brain of human embryo 69 mm. long (more than 5 weeks). (Redrawn from Kollmann's *Handatlas*.)

myelencephalon. The motor fibers of these nerves arise from neuroblasts in the ventral plate, where the motor nuclei of these nerves develop in a region corresponding to the ventral gray column of the spinal cord. Their sensory fibers arise from neuroblasts in the adjacent ganglia, whence they grow into the dorsal plate, a region corresponding to the dorsal gray column of the spinal cord (Fig. 167). The development of the individual nerves will be treated in a later section.

2. Development of the Metencephalon. From the metencephalon the cerebellum and the pons develop (Fig. 166). In this division of the brain the roof plate again becomes narrow. This condition allows the two dorsal plates to come together in the mid line in such a manner as to form a transverse ridge across the dorsal side of the neural canal. This ridge is the rudiment of the cerebellum (Figs. 162 and 163). In this ridge two swellings form near the mid line, the rudiments of the vermis, and two in a more lateral position, the rudiments of the cerebellar hemispheres. These rudiments grow greatly in volume, and at the same time their surfaces become folded to form the convolutions of the cerebellum (Figs. 164, 165, and 166).

The cortex is formed by the migration of cells from the mantle

5 Development of the Telencephalon The telencephalon gives rise to by far the greater part of the adult brain, as is clearly seen in Fig 166. The telencephalon consists at first of the small, rounded anterior end of the neural tube (Fig 161) from which median portion the two cerebral hemispheres soon begin to grow out dorso-laterally (Fig 162). The telencephalon thus comes to include a median portion and two hemispheres (Fig 159).

The median part contains the anterior end of the third ventricle and is essentially a continuation of the diencephalon, there being no line of demarcation between these two divisions in the adult (Fig 166). The anterior wall of the median portion becomes the lamina terminalis, which accordingly marks the most anterior part of the neural tube (Figs 159 and 166).

The Cerebral Hemispheres The cerebral hemispheres grow to great size and become by far the largest part of the human brain. So great is their growth that, though they arise as outgrowths of the telencephalon, they later become connected also to the sides of the diencephalon and mesencephalon, so that these three divisions of the brain become united into a composite structure known as the cerebrum. Into the hemispheres extend portions of the neural canal, which become the lateral ventricles. Each lateral ventricle communicates with the third ventricle by the interventricular foramen (foramen of Monro) (Figs 159 and 166). The choroid plexus of the lateral ventricles develops in the thin roof plate and extends far into the hemispheres. The development of the hemispheres involves the history of (1) the corpora striata, (2) the pallium, and (3) the rhinencephalon.

1 THE CORPORA STRIATA Early in development the two corpora striata form, each as a thickening of the floor of one of the lateral ventricles. These masses at their caudal ends are closely connected with the thalamus and later fuse with them. From the corpora striata develop the caudate and lenticular nuclei, which become separated from each other by the internal capsule, a sheet of nerve fibers connecting the thalamus and other lower nuclei of the brain with the cerebral cortex.

2 THE PALLIUM The dorsal and lateral walls of the hemispheres are known as the pallium, a region of great importance, because here develops the cerebral cortex, the structure which attains such high development in the human brain. This cortex develops, as does that of the cerebellum, by the migration of neuroblasts from the mantle layer into the marginal layer, where they develop into the gray matter, composed of the pyramidal cells and others of the cortex. The white

remains thin and becomes much folded. Into its folds grows a dense network of blood vessels to form the **choroid plexus** (the **velum interpositum**) of the third ventricle. From the thickened side walls which include the dorsal plates only (see p. 238), the **geniculate bodies** and

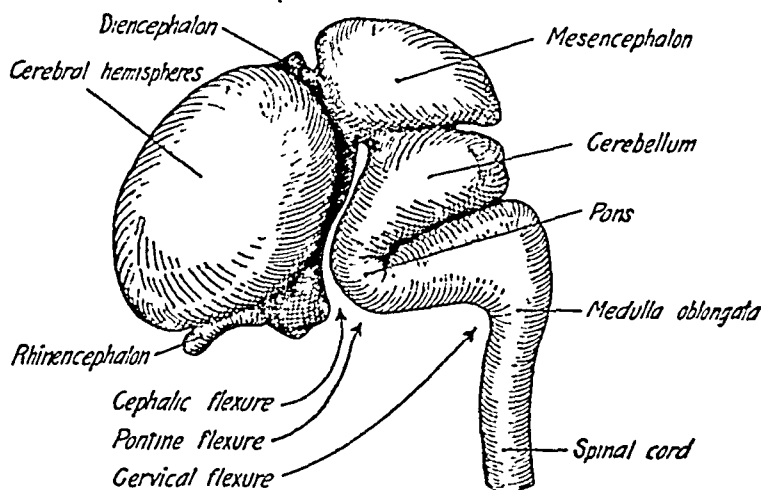


FIG. 164. Lateral view of brain of human embryo 22 mm. long (nearly 8 weeks). (Redrawn from Kollmann's *Handatlas*.)

the thalami develop; the thalami often fuse across the cavity of the third ventricle to form the **massa intermedia**. More ventrad there are formed the **corpora mammilaria** and the **tuber cinereum**. The optic evaginations which develop into the retinas and the optic nerves are

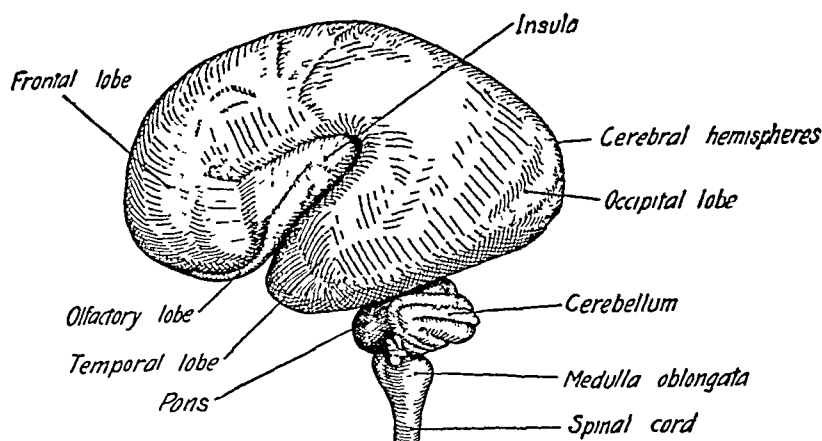


FIG. 165. Lateral view of brain of human fetus 6 months old. (Redrawn from Kollmann's *Handatlas*.)

also outgrowths from this division of the brain (Figs. 161 and 162). From the floor are derived the **infundibulum** and the **pars nervosa** of the **hypophysis**. It will be remembered that the **pars buccalis** of the **hypophysis** develops from the ectoderm of the oral pit (see p. 133).

campi, forming the hippocampal commissure, and in part of other fibers which pass without crossing through the columns of the fornix to the corpora mammilaria (3) The corpus callosum appears at first as a small band of fibers in the roof of the lamina terminalis. As its fibers become more numerous, it expands until it becomes a great sheet of fibers coursing between the two hemispheres (Fig 166)

The Development of the Cranial Nerves

The cranial nerves do not exhibit the uniformity which characterizes the spinal nerves, either in adult structure or in the manner of development. Just as the head does not have a well-developed segmentation like that of the trunk, so its nerves also lack the definite segmental relations of the spinal nerves. The cranial nerves are not to be considered a continuation of the spinal series, except in a very loose sense.

There are certain similarities, however, between the two sets of nerves in their structure and manner of development, because of these similarities a knowledge of the spinal nerves promotes a better understanding of the cranial nerves. The cranial nerves have the same four functional components which make up the spinal nerves: somatic motor, somatic sensory, visceral motor, and visceral sensory, but with the difference that no cranial nerve has all four components.

In the cranial nerves the fibers of these components develop essentially as they do in the spinal nerves. The motor fibers arise from neuroblasts located in the basal plate of the neural tube, mainly in the region of the myelencephalon. In the basal plate of the brain region two definite sets of motor nuclei develop: ventral nuclei near the median line and lateral nuclei less close to it (Fig 167). From the ventral nuclei develop the *somatic motor fibers*, and from the lateral nuclei the *visceral motor*. The sensory fibers, except those of the olfactory and optic nerves, develop from neuroblasts in the cranial ganglia (Fig 167).

It should also be noted that, in addition to the four components just described, there are certain cranial nerves (olfactory, optic, and auditory) which do not belong to any of these groups and are not represented in the spinal nerves. These are designated as *special sensory nerves*.

The cranial nerves do not all belong to one series of similar nerves, as do the spinal, but rather fall into three different groups: (1) *special sensory*, (2) *somatic motor*, and (3) *mixed nerves* developed in connection with the pharynx.

matter of the hemispheres is composed of nerve fibers which grow from neuroblasts in the cortex and in the lower centers of the brain. These fibers become so numerous that the walls of the hemispheres grow very thick, and the ventricles become relatively small. Until about the beginning of the sixth month the surface of the hemispheres

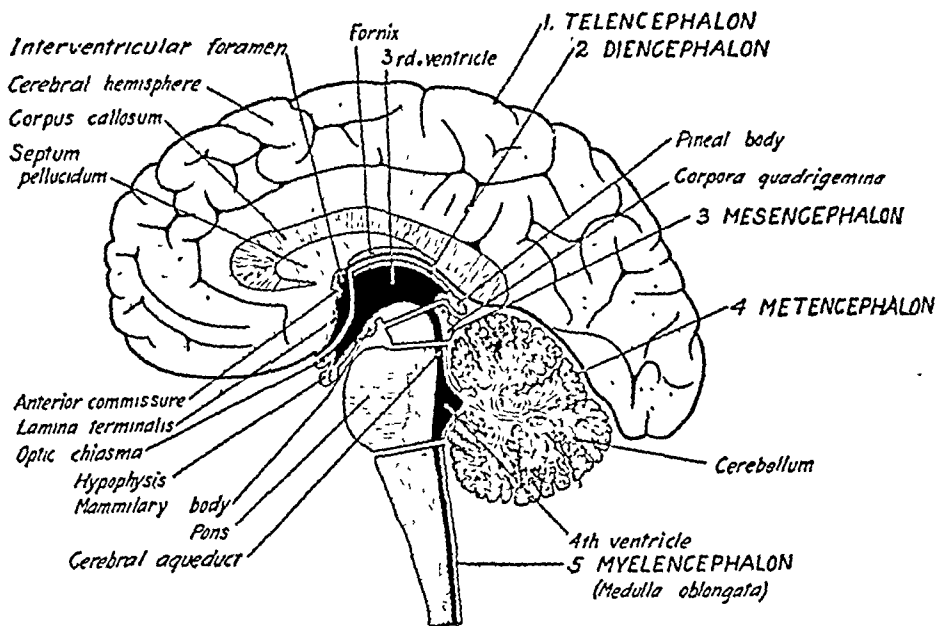


FIG. 166. Outline sketch of mid-sagittal section through adult human brain, divided into five parts to show the adult derivatives of the five embryonic divisions.

is smooth (Figs. 164 and 165), after which period the convolutions and fissures form rapidly, and by the time of birth the adult topography is well established.

3. THE RHINENCEPHALON. The rhinencephalon (olfactory brain) in lower vertebrates forms the greater part of the hemispheres. In human development it arises as a swelling, the **olfactory lobe**, on the ventral side of each developing hemisphere (Figs. 164 and 165). It gives rise to the olfactory bulb and tract, together with other inconspicuous parts, all connected with the sense of smell.

The Commissures of the Telencephalon. There are three commissures connecting the two sides of the telencephalon, formed by fibers which grow across from one side to the other: (1) The **anterior commissure** is a small band passing through the lamina terminalis and connecting mainly between the olfactory bulbs (Fig. 166). (2) The **fornix** is composed in part of fibers crossing between the two hippo-

II The Optic Nerve The fibers of the optic nerve grow from neuroblasts in the retinal layer of the optic cup, following the optic stalk into the brain (Fig 177, p 264) Since the optic cup is an extension of the neural tube, the optic nerve is in reality not an external nerve at all, but a tract within the brain

VIII The Auditory Nerve The auditory nerve fibers grow from neuroblasts in the auditory ganglion, the rudiment of which lies close to the otocyst on its anterior side (Fig 178B, p 267) Its neuroblasts

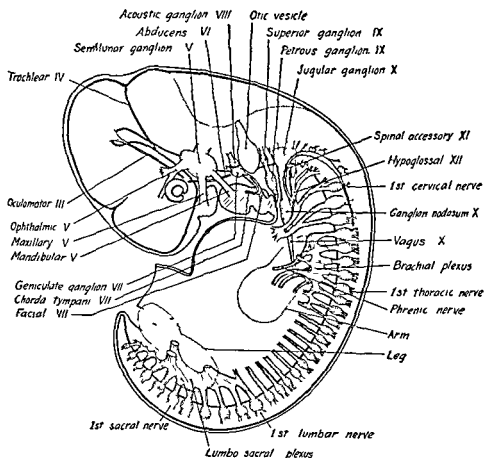


FIG 169 Outline drawing to show the spinal and cranial nerves which have developed in a human embryo 10 mm long (6 weeks) (Redrawn from Streeter in *Am Jour Anat*)

give rise to bipolar cells, one process of which grows into the myelencephalon, whereas the other comes into close relation with the epithelium of the otocyst (Fig 167) As the ganglion develops it divides into two parts, which give rise to the vestibular and spiral ganglia of the inner ear This ganglion has its origin from a portion of the neural crest Thus in its mode of development the auditory nerve is like the

1. The Special Sensory Nerves

These nerves, which supply the three organs of special sense, do not have any exact equivalent in the spinal nerves or other cranial nerves,

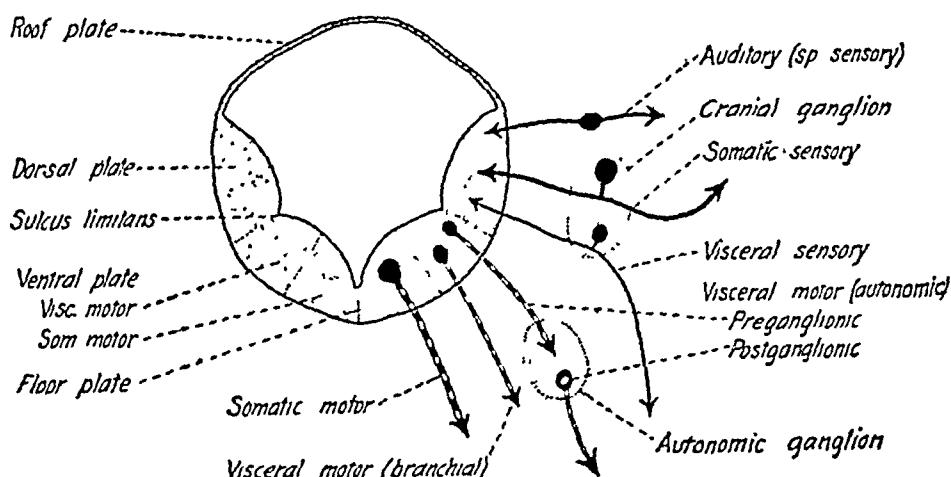


FIG. 167. Diagrammatic cross-section through the medulla oblongata, showing the nuclei of origin of the various functional components of the cranial nerves. The arrow heads show the direction of growth of the fibers. Compare this figure with Fig. 158.

inasmuch as they do not belong either to the visceral sensory or to the somatic sensory nerves of the general cutaneous type. Neither are these nerves equivalent to each other, as will be evident after a description of their development.

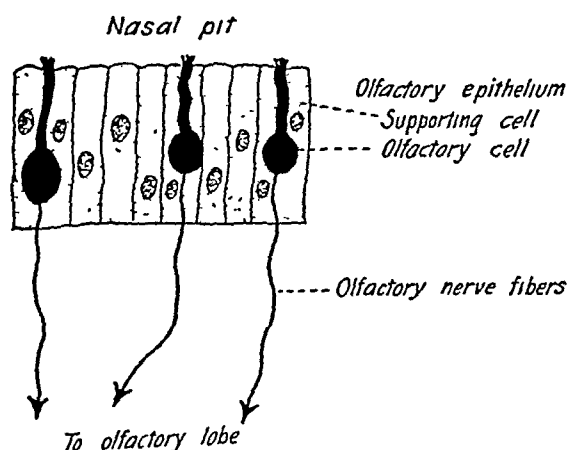


FIG. 168. Diagram to show the mode of origin of the fibers of the olfactory nerve from neuroblasts located in the olfactory epithelium.

is unique in that its fibers do not grow from cells of the neural tube or neural crest, but from cells of the surface ectoderm of the body.

I. The Olfactory Nerve. The fibers of the olfactory nerve develop as outgrowths from certain ectodermal cells lining the olfactory pits, in the region which becomes the olfactory mucosa. Axones from these cells grow into the olfactory lobe of the brain, where they come into relation with the neurones of the olfactory tract (Fig. 168). The olfactory nerve

sensory and motor There are two kinds of motor fibers (1) those which distribute through the autonomic system to the muscles and glands of the alimentary canal and other viscera, and (2) those which supply the striated voluntary muscles which develop in the wall of the pharynx These latter fibers go directly to the muscles instead of through the autonomic system The nerves of the pharynx also include some somatic sensory fibers, which supply the sense organs of the integument of the branchial region and head generally

There are no somatic motor fibers in these nerves, because the striated muscles of the jaws and face are not derived from myotomes, but from the mesenchyme of the pharyngeal wall For this reason these muscles correspond developmentally to the involuntary muscles of the intestinal tract, not to the voluntary muscles of the trunk and limbs This fact explains why their nerve supply is from visceral rather than somatic nerves

The motor components of these nerves arise from neuroblasts in the lateral nuclei of the basal plate of the myelencephalon, and the sensory parts from cells in the adjacent ganglion masses (Fig 167)

V The Trigeminal Nerve The trigeminal is the nerve of the first arch, the arch which gives rise to the bones of the jaws and the muscles of mastication (Fig 169) This nerve, though mixed, is largely sensory Its sensory fibers are outgrowths from cells in the large semilunar ganglion The fibers which grow centrad form the large nerve connecting the ganglion with the brain, and those which grow peripherad form the three large branches, the ophthalmic, the maxillary, and the mandibular nerves These three nerves are mainly composed of somatic sensory fibers which supply the sense organs of the skin covering the face and the top of the head (Fig 170) They also supply the teeth and the oral and nasal cavities, which are derived from the ectoderm of the oral and nasal pits It will be observed by comparing Figs 31, p 50, and 170 that the area supplied by the ophthalmic nerve corresponds in the main to the part of the face derived from the naso-frontal process, that supplied by the maxillary to the region derived from the maxillary process, and that supplied by the mandibular to the region derived from the mandibular process There are a few sensory fibers, which are probably visceral, going to the region of the first arch (the epithelium of the palate and tongue) The motor fibers of the trigeminal nerve are confined to a small portion of the nerve, which runs a rather independent course from the brain and is sometimes called the masticator nerve It supplies the muscles of mastication and others derived from the first arch

VII The Facial Nerve The facial nerve belongs to the second arch

sensory portion of the spinal nerves and of the cranial nerves of the pharyngeal region, but is unlike the olfactory and optic nerves.

2. *The Somatic Motor Nerves*

The four nerves included in this group have but one component each, except for a small visceral motor element in the oculomotor. Their fibers develop from the ventral nuclei of the basal plate (Fig. 167), from which fact it is evident that they correspond to the somatic motor parts of the spinal nerves and the other cranial nerves.

III. The Oculomotor Nerve. The fibers of the oculomotor nerve arise from neuroblasts in the basal plate of the mesencephalon and become connected with four of the six extrinsic muscles of the eyeball (Fig. 169). This nerve also includes a small component of autonomic fibers to the ciliary ganglion, which sends axones to muscle fibers within the eyeball.

IV. The Trochlear Nerve. The fibers of the trochlear nerve arise from neuroblasts in the basal plate of the mesencephalon just caudad to the oculomotor. The peculiarity of this nerve is that its fibers do not emerge from the neural tube ventrally, but grow dorsad and cross in the roof plate of the tube before emerging, whence they grow to connect with the superior oblique muscle of the eye (Fig. 169).

VI. The Abducens Nerve. The fibers of the abducens nerve arise from neuroblasts in the basal plate of the myelencephalon. They emerge ventrally and grow cephalad to reach the external rectus muscle of the eye (Fig. 169).

XII. The Hypoglossal Nerve. The hypoglossal is the cranial nerve that shows least departure from the spinal type, being formed by the combined ventral roots of three spinal nerves, the dorsal roots of which do not develop (Fig. 169). Its fibers grow craniad and reach the muscle fibers of the tongue. Early in its development this nerve unites with the first three cervical nerves to form the *ansa hypoglossi*.

3. *The Mixed Nerves in the Pharyngeal Region*

The remaining five cranial nerves are mixed, each one including two or three of the four components of the spinal nerves, the somatic motor type alone being lacking. These nerves develop in connection with the pharynx, and in the embryo exhibit a segmentation corresponding to the branchial arches. During development, however, differential growth and migration of structures derived from the branchial arches obscure to some extent the original relations and leave doubt concerning certain nerves.

The nerves of the pharyngeal region include visceral fibers, both

IX The Glossopharyngeal Nerve The glossopharyngeal is the nerve of the third arch (Figs 169 and 170) Its motor fibers supply the stylopharyngeus muscle of the pharynx Motor fibers, by way of the otic ganglion (autonomic), supply the parotid gland Its sensory

TABLE 6

THE COMPONENTS OF THE CRANIAL NERVES

Nerves	Special Sensory	Somatic Motor	Somatic Sensory	Visceral Motor		Visceral Sensory	
				Bran- chial	Auto- nomic	Bran- chial	Auto- nomic
I Olfactory (to nose)	x						
II Optic (to retina)	x						
VIII Auditory (to ear)	x						
III Oculomotor (to myo- tome)		x			x		
IV Trochlear (to myo- tome)		x					
VI Abducens (to myo- tome)		x					
XII Hypoglossal (to tongue)		x					
V Trigeminal (to first arch)			x	x		x	
VII Facial (to second arch)				x	x	x	
IX Glossopharyngeal (to third arch)				x	x	x	
X. Vagus (to fourth and fifth arches and vis- cera)			x	x	x	x	x
XI Spinal accessory (to fourth and fifth arches and viscera)				x	x		

(Fig. 169). Though a mixed nerve, it is almost wholly visceral motor. In the embryo its motor part is short and not large; it supplies merely the second arch, which at first is not a large structure. As the development and migration of the muscles of expression progress, the nerve extends and spreads with the muscles until it reaches far beyond the limits of the pharynx, spreading widely over the face and scalp (Fig. 170). It will be observed that this nerve supplies the motor fibers to

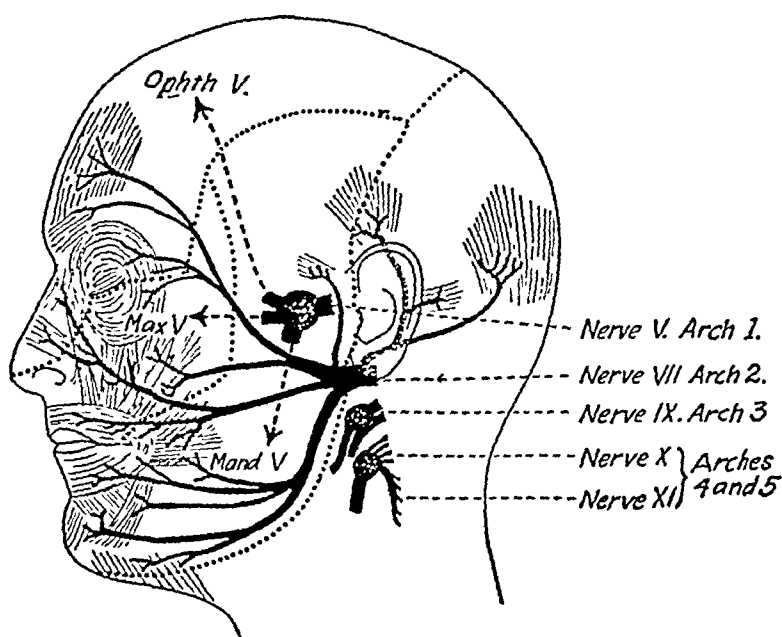


FIG 170. Outline of adult head, showing, in somewhat diagrammatic manner, the cranial nerves belonging to the branchial arches. The areas of skin supplied by each of the three branches of the trigeminal nerve (first arch) are outlined. The general distribution of the facial nerve (second arch) is shown and most of the muscles derived from this arch, as well as the stumps of the nerves of the third, fourth, and fifth arches.

muscles which, in general, underlie the areas of skin which receive their sensory fibers from the trigeminal nerve of the first arch. These muscles also overlie the muscles of mastication derived from the first arch and supplied by the trigeminal nerve. So extensive has been the migration of the muscles and nerves derived from the second arch that their adult position gives very little hint of their embryonic derivation.

The motor portion of the facial nerve supplies also the submaxillary and sublingual glands, through the submaxillary ganglion, which belongs to the autonomic system. Its small visceral sensory part supplies the taste buds of the anterior two thirds of the tongue. These sensory fibers are outgrowths from neuroblasts in the geniculate ganglion.

ing man, some observers state that the placodes contribute to the ganglia, whereas others have been unable to satisfy themselves that such contribution occurs. On the whole, it seems a safe conclusion that, although in the main the human cranial ganglia are derived from the neural crest, in all probability they also receive contributions from the epibranchial placodes.

E THE DEVELOPMENT OF THE AUTONOMIC SYSTEM

The autonomic system, often called the sympathetic system, includes two portions, now generally designated as thoracolumbar (sympathetic) and craniosacral (parasympathetic) portions.

For an understanding of the autonomic system it must be remembered that there are not two nervous systems, cerebrospinal and autonomic, but that these two are merely portions of one system. The autonomic portion supplies glands and involuntary muscle wherever located. It is closely associated, accordingly, with the organs of the thoracic and abdominal cavities, but it also extends throughout the whole body to the involuntary musculature of all blood vessels and to the muscles and glands of the skin.

The structural peculiarity of the autonomic system lies in the fact that the motor fibers which make up the system do not run continuously from the brain or spinal cord to the muscles or glands, as do the fibers to voluntary muscles. On the contrary, the autonomic motor path is composed of two sets of neurones: (1) the preganglionic neurones, located in the central nervous system, with axones passing to the autonomic ganglia, and (2) the postganglionic neurones, located in the autonomic ganglia, with axones extending to the glands and involuntary muscles. The autonomic ganglia are composed of the cell bodies of the postganglionic neurones (Figs 158 and 167).

There are three sets of autonomic ganglia in cervical and trunk regions: (1) those of the sympathetic trunks, (2) those of prevertebral plexus, and (3) the terminal ganglia in the wall of the alimentary canal and other viscera. In addition there are four autonomic ganglia in the head which are associated with certain cranial nerves.

The nerves of the autonomic system include: (1) the *rami communicantes*, both gray and white, which connect the spinal nerves with the ganglionated cords, (2) the two longitudinal, ganglionated cords, (3) parts of certain cranial nerves, and (4) nerves connecting the many ganglia and distributing to the organs. The development of the autonomic system will be treated in the following paragraphs, where it will be seen that this system has a very close anatomical relation to the cerebrospinal system.

fibers distribute to the middle ear, pharynx, and posterior third of the tongue. They arise from cells in its two ganglia, the root ganglion and the petrosal or trunk ganglion.

X. The Vagus Nerve. The vagus nerve develops in relation to the *fourth and fifth arches* (Figs. 169 and 170). It sends visceral motor fibers to the voluntary muscles of the soft palate, pharynx, and larynx; it sends a few somatic sensory fibers to the skin of the ear, and visceral sensory fibers to the pharynx, larynx, and esophagus. In addition, the vagus has other large visceral portions, both sensory and motor, which distribute widely to the thoracic and abdominal viscera through the autonomic system. The vagus is a composite nerve, representing the nerves to several branchial arches of aquatic vertebrates. It has, accordingly, several root ganglia, the most anterior one being the largest (the jugular ganglion). The large ganglion *nodosum* of the trunk of the nerve when first recognized is not connected with the root ganglia. The sensory fibers of the nerve are outgrowths from cells in these ganglia.

XI. The Spinal Accessory Nerve. The spinal accessory nerve belongs to the *fourth and fifth arches* (Fig. 169). It is exclusively visceral motor. One portion of this nerve, the accessory vagus, develops in close relation to the vagus and is distributed in company with it; it contains visceral motor fibers for the pharynx and larynx and also extensive visceral motor fibers which reach to the thoracic and abdominal viscera by way of the autonomic system. The spinal part of the nerve develops from neuroblasts in the region of the first four cervical segments (Fig. 169). These fibers unite to form a trunk, which supplies the trapezius and sternocleidomastoid muscles (see p. 114).

The Sensory Ganglia of the Cranial Nerves

The ganglia of the trigeminal, facial, auditory, glossopharyngeal, and vagus nerves are essentially similar in their development to the dorsal root ganglia of the spinal nerves (p. 230), in that they have their origins from the neural crest. The development of the sensory cranial ganglia, however, is complicated by the probable addition to the early ganglionic masses of other cells from thickened areas of the overlying ectoderm (known as epibranchial placodes), lying just dorsal to the branchial grooves. The early ganglionic masses from the neural crest are seen to come into intimate contact with the placodes, and there is general agreement that, in the lower groups of vertebrates, cells from the placodes are added to the ganglia, making an important contribution to their structure. In mammals, includ-

and the pia mater) develop from mesenchyme. Within recent years, however, experimental studies on larvae of amphibia, together with observations on embryos of chick and pig, have convinced some workers that, although the dura mater develops from mesenchyme as generally believed, the arachnoid and the pia mater develop from ectodermal cells which migrate from the neural crest. Such a view is a radical departure from current belief and would place these two membranes developmentally with the neurilemma sheath and not far from the neuroglia tissue, rather than with the mesodermal connective tissues.

G THE DEVELOPMENT OF THE SUPRARENAL GLANDS

The suprarenal glands are located just above the kidneys, from their position their name is derived. They have no other relation to the kidneys, either functionally or developmentally. Their development is taken up at this place because of their intimate embryological relation to the autonomic nervous system.

In embryonic development the cortex and medulla of the suprarenal gland have entirely different origins and only secondarily do they unite into one organ.

The epithelial cells of the cortex of the suprarenal gland are derived from an area of mesothelial cells in the peritoneal epithelium on either side of the base of the mesentery. The mesothelial cells of these areas become columnar, undergo mitotic multiplication, and migrate into the underlying mesenchyme. There are two successive proliferations of these cells. (1) In embryos of 7-8 mm (like that in Fig. 23, p. 46, age about five weeks) the proliferating cells become rather large and have acidophil staining reaction. These develop into the fetal cortex. (2) In embryos of 11-13 mm (six to six and one-half weeks) a second proliferation begins, which produces smaller cells with basophil reaction. These become the permanent cortex, which when first formed is a superficial layer largely surrounding the fetal cortex (Fig. 171).

The epithelial cells of the medulla (the chromaffine cells) are ectodermal cells which migrate from the primordia of the ganglia of the sympathetic trunk and become glandular cells instead of nerve cells. These cells first take their position on the medio-ventral side of the developing cortex, and in embryos of about 13-14 mm (six and one-half to seven weeks) they begin to invade the cortical mass (Fig. 171), the process continuing until the chromaffine cells are entirely surrounded by the cortical cells.

A striking feature of the development of the suprarenal gland is its

The Autonomic Ganglia. Until rather recently it has been universally believed that the autonomic ganglia develop from cells which migrate from the neural crest. Investigations of rather recent years, however, seem to indicate that the neuroblasts which form the autonomic ganglia (with the possible exception of those in the head) migrate from the ventral (motor) plate of the neural tube at an early stage. These migrant cells undergo multiplication in their new locations and later develop into multipolar neurones, as do the neuroblasts in the neural tube. Possibly the question of origin is not yet settled, and the reader should not be unduly confused by conflicting statements he is sure to find in the literature.

The neuroblasts which form the ganglia of the thoracolumbar portion migrate along the ventral roots of thoracic and lumbar spinal nerves to form the ganglia of the sympathetic trunk and the prevertebral plexus. Those which form the craniosacral portion come mainly from the hind brain, migrating along the vagus nerves, with a much smaller contribution from the sacral spinal cord by way of appropriate spinal nerves. These neuroblasts form the terminal ganglia in the walls of the visceral organs. The development of thoracolumbar and craniosacral parts takes place in such a way that almost all glands and involuntary muscles receive their nerve supply from both of them.

The Autonomic Nerves. The autonomic nerves include fibers from two sources: (1) preganglionic motor axones which grow out from neuroblasts in the intermedio-lateral gray column of the spinal cord or the lateral nuclei of the brain; and (2) postganglionic motor axones from neuroblasts in the autonomic ganglia (Figs. 158 and 167). The autonomic nervous system consists essentially of these two sets of motor neurones. The sensory fibers from visceral structures are not considered part of the autonomic system.

Those axones which originate from neuroblasts in the neural tube (preganglionic axones) become medullated; those from neuroblasts in the autonomic ganglia usually do not. Accordingly, the preganglionic motor axones in the ventral roots of the spinal nerves and in the white rami communicantes are medullated, as are also those in the vagus and spinal accessory nerves (Figs. 158 and 167). On the contrary, the postganglionic axones of the gray rami communicantes are non-medullated, as are also the numerous autonomic axones which supply involuntary muscle and glandular tissue (Figs. 158 and 167).

F. THE DEVELOPMENT OF THE MENINGES

The general view through the years has been that the fibrous coverings of the central nervous system (the *dura mater*, the *arachnoid*,

H ANOMALIES

A conspicuous group of monstrosities is produced by failure of the neural tube to close. The failure may involve extensive or restricted regions. Inasmuch as the closure of the tube normally takes place very early in development (during the fourth week), its non-closure must produce serious defects in structures closely related to the neural tube, especially the associated skeletal parts. Failure of the closure in the cranial region results in absence, not only of the brain, but also of

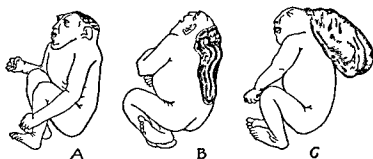


FIG 172 Three types of human monster characterized by defects in the neural tube A, anencephalic acrania Brain and cranial vault wanting B, craniorachischisis The defect extends also the length of the spinal cord C, exencephalic acrania The meninges and sometimes the cerebral hemispheres, form a pendulous mass filled with fluid (Redrawn from Nafagias in *Am Jour Anat*)

the cranial vault, producing an acranial monster, whose head consists almost wholly of the face. Sometimes the defect extends also to the region of the spinal cord and vertebral column. Various forms of this monstrosity exist, but all have a common, characteristic appearance. This is by all means the most frequent form of conspicuous monstrosity which commonly comes to full term. Death follows quickly after birth. The general appearance of three types is shown in Fig 172.

Hydrocephaly is a great enlargement of the head due to excessive fluid in the ventricles of the brain. Microcephaly involves very small development of the brain, though the head is often not conspicuously deformed.

large size during the fetal months, so that for a considerable time the gland is larger than the kidney (Fig. 153, p. 225). It undergoes a great reduction in size during the weeks immediately after birth, and not until puberty does it again attain the size it had at birth.

The large size during prenatal life is due to the great growth of the fetal cortex, which during these months forms by far the greater portion of the gland. During the first year after birth, however, the fetal cortex wholly degenerates, and the cells of the surrounding permanent cortex invade the vacated area. The fetal cortex has been the object of considerable recent study, but its special function is not yet certain. It has been called the "X-zone" and the "androgenic zone"; the latter term is applied because of some evidence that the fetal cortex secretes a male hormone which protects the fetus against undue influence from the female hormones reaching it from the mother through the placenta.

Not all the chromaffine cells become incorporated into the suprarenal glands, but some of them, chief among which are the two inter-carotid ganglia (often called carotid glands) and the two aortic

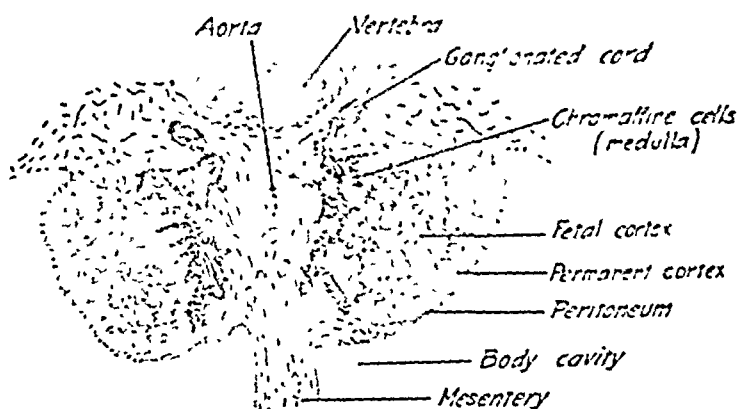


FIG. 171. The suprarenal glands as in a human embryo 17 mm. long. Chromaffine cells just beginning to penetrate the cortical mass. (Outline from Zukerkandl in Keibel and Mall, *Human Embryology*; divisions of cortex from Uotila in *Anat. Rec.*)

chromaffine bodies, persist as independent bodies. Still other chromaffine cells do not become separated from the sympathetic ganglia, many of the adult ganglia containing small masses of this tissue. Neither does all the cortical substance always remain connected with the two main glands; fragments of it often become separated from the main mass in early stages to form the accessory suprarenals which may be found among the genital organs and elsewhere.

3 Specialized Epithelial Sensory Endings In several of the important sensory organs the nerve fibers terminate in specialized epithelial areas, some of them derived from ectoderm and others from entoderm. All these epithelial sensory endings have a common developmental plan, in that from the primitive epithelium two kinds of cells develop (1) supporting (sustentacular) cells and (2) sensory cells with hair-like processes at their free ends. In the crista, macula, organ of Corti, and taste buds the terminal branches of sensory nerve fibers grow out from neuroblasts in the sensory ganglia and develop intimate contact with the sensory cells. The olfactory epithelium differs in that the nerve fibers develop as cytoplasmic outgrowths from the basal ends

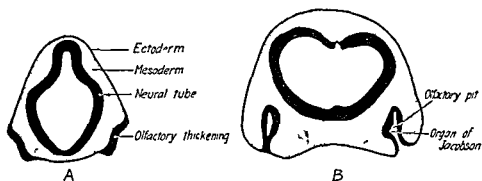


FIG 173 Early stages of the olfactory organ *A*, section through head of pig embryo 6 mm long *B*, section through head of pig embryo 9 mm long. The two olfactory pits are not both cut at the same level, so that the opening of only one of them is shown.

of the sensory cells, whence they grow toward the brain, forming the olfactory nerve (Fig 168). An epithelium such as those listed above is commonly designated as a *neuro-epithelium*. The complicated organs in which these sensory structures lie are described on pp 259 to 273.

4 Sensory Structures of Nervous Origin The retina of the eye is unique, in that the sensory cells (rod cells and cone cells) are essentially nerve cells, inasmuch as the retina develops from an outgrowth of the neural tube (see p 260).

B THE ORGAN OF TASTE

The taste buds are local specializations of the entodermal epithelium of the pharynx. They develop in relation to the gustatory fibers of the facial, glossopharyngeal, and vagus nerves on the surface of the tongue and in adjacent pharyngeal regions (for development of tongue, see pp 134 and 135). The two kinds of epithelial cells are the

CHAPTER XIX

THE SENSE ORGANS

Under the heading of sense organs (receptors) are included not only the more complicated organs for vision, hearing, and other sensory functions but also all nerve terminations which have to do with the reception of stimuli, either external or internal, whether these nerve endings are located superficially or within the deeper organs of the body.

The adult sense organs are exceedingly varied, and some of them are highly complicated, including elaborate structures which convey the several kinds of stimuli to the sensory cells through which the sensory nerve impulse is initiated. In nearly all types of sensory nerve endings, however, the essential relations are the same: namely, the terminal arborizations of the afferent nerve fibers come into intimate contact with sensory cells of some sort. It is only in the development of the accessory structures that the embryology of sense organs becomes complicated.

The development of motor (efferent) nerve endings might well be described here also, because in their development there is nothing outstanding to differentiate them from sensory endings. Their development involves only the branching of the efferent axones to form terminal arborizations which establish intimate relations with effector structures, namely, muscle fibers and epithelial cells of glands.

A. GENERAL TYPES OF SENSORY NERVE ENDINGS

The following classification is purely anatomical and developmental, with no reference to physiological types.

1. **Free Sensory Endings.** This is the simplest type of sensory ending. No specialized sensory cells develop, but the branched nerve terminations lie among epithelial cells (chiefly in the epidermis), in the connective tissue below the epithelium, or in muscle or tendon.

2. **Encapsulated Endings in Connective Tissue.** Several types of sensory structures develop as local specializations of mesenchyme to form connective tissue capsules of various forms and complexities, in which the nerve fibers terminate. Among these are the corpuscles of Meissner, Ruffini, and Golgi-Mazzoni, the Pacinian corpuscles, the end bulbs of Kraus, and muscle and tendon spindles.

its outer surface, like a hollow rubber ball with one side pushed in. This process continues until the two walls come into contact, and the bulb is changed into a double-walled, cup-like structure, the *optic cup* (Fig 175). The invagination which forms the optic cup is not symmetrical but proceeds in such a manner as to leave a cleft, the *choroid*

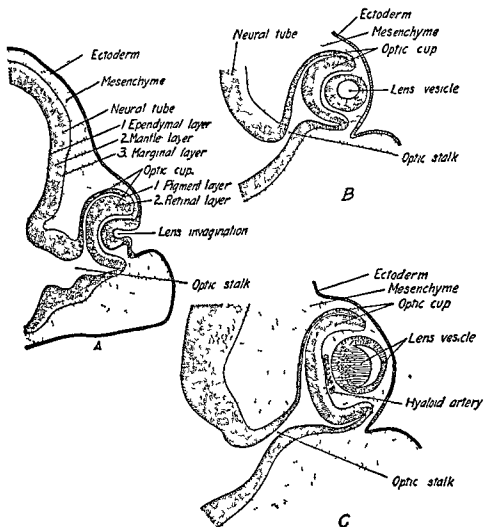


FIG 175 Three phases of the development of the eye, as seen in sections through the head of pig embryos. Somewhat diagrammatic. A, embryo 6 mm long; B, 9 mm; C, 12 mm.

fissure, in one side of the cup, extending from rim to base (Fig 176). The choroid fissure also extends for a distance along the optic stalk. The choroid fissure normally closes during the sixth or seventh week. As the optic cup grows larger, its open end becomes relatively smaller, until the structure takes the form of a double-walled, hollow sphere with only a small hole, the future pupillary opening, at its distal side.

supporting cells and the sensory gustatory cells. Taste buds begin to develop about the third month.

C. THE ORGAN OF SMELL

The general development of the nose, including both its cavities and its skeletal elements, is described in Chapters V, VIII, and XI. The nasal epithelium is ectodermal. The sensory olfactory epithelium develops in the superior meatus, a part of the olfactory pits (Figs. 89, p. 130, and 173). The cells of this epithelium differentiate into the supporting cells and the sensory olfactory cells. From the olfactory cells grow the fibers of the olfactory nerve (Fig. 168, p. 246).

The organs of Jacobson are a pair of small pits which form in the nasal septum near its lower, anterior edge (Figs. 173 and 88, p. 129). The epithelium of these pits develops for a time like that of the olfactory region, producing axones which join the olfactory nerve, but the whole structure often wholly degenerates in late fetal life, though it sometimes persists in the adult. It is a well-developed organ in some other mammals, but it is apparently functionless in man.

D. THE EYE

The Eyeball

The eyeball includes parts from both ectoderm and mesoderm. The ectodermal parts are derived from three embryonic sources: (1) the optic vesicle, (2) the lens vesicle, and (3) a part of the ectoderm covering the head of the embryo. The mesodermal parts develop from the mesenchyme immediately surrounding the optic cup.

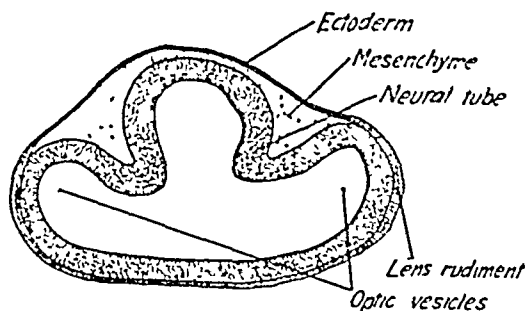


FIG. 174. The early eye vesicle, as seen in cross-section through head of chick embryo with 12 somites.

The Derivatives of the Optic Vesicles. In embryos of about 2.5 mm. (four weeks) the optic vesicles begin to form as a pair of lateral outgrowths from the neural tube in the region that will become the diencephalon (Figs. 161 and 174). The optic vesicles soon become differentiated into a larger, distal portion, the bulb, and a narrower part, the optic stalk, which connects the bulb to the neural

tube. The cavities of the bulb and stalk are continuous with that of the neural canal (Fig. 174). Then the optic bulb becomes indented on

fissure to enter the optic stalk (Fig 177) In the mantle layer of the optic stalk they grow into the brain as the fibers of the optic nerve The original cells of the optic stalk develop into the supporting cells of the optic nerve

The Ciliary Body and the Iris The two epithelial layers of the optic cup in the region of the pars caeca largely retain their primitive epithelial condition and become the two-layered pigmented epithelium covering the folds of the ciliary body and the posterior surface of the iris (Fig 177) Some of the cells of the pigment layer develop into the contractile fibers of the sphincter and the dilator muscles of the iris, one of the rare examples of muscle tissue developed from ectoderm

The remaining parts of the ciliary body and iris develop from mesoderm (Fig 177) In the region of the ciliary body mesenchyme forms in considerable amount and develops into the stroma and the smooth muscle fibers These mesodermal parts are a direct continuation of the choroid coat, just as the epithelial covering is a continuation of the retinal layer The stroma of the iris and its anterior epithelium are likewise developed from mesenchyme The opening of the optic cup becomes the pupillary opening

The Vitreous Body The vitreous body was formerly thought to be a derivative of mesenchyme which enters the optic cup through the choroid fissure Now, however, it seems more probable that it arises as an exudate from the retinal layer of the optic cup, and that the fibers of the suspensory ligament of the lens are also formed by the ectodermal cells of the ciliary part of the optic cup

The Lens Vesicle and the Lens While the optic cup is still in a very early stage of development, the lens placode begins to form as a thickening of the ectoderm covering the surface of the head in a spot just opposite the optic bulb (Fig 174) This thickened ectoderm becomes depressed until it forms a closed sac, which separates entirely from the parent ectoderm as the lens vesicle (Fig 175) The lens vesicle at first lies in the open end of the optic cup and finally takes its place just inside the pupillary opening, in which position it develops into the lens (Figs 176 and 177)

The wall of the lens vesicle is at first of uniform thickness, but soon the cells of the outer or front half cease to grow, whereas those of the posterior wall become very tall and wholly obliterate the cavity of the vesicle (Figs 175 and 177) These elongated cells become the transparent lens fibers, which make up the mass of the lens, and the cells of the thinner, front wall become the lens epithelium

The Mesodermal Parts of the Eyeball The optic cup and the lens vesicle are, from the first, surrounded by the loose mesenchyme of the

The Retina. Meanwhile the inner layer of the cup, known as the nervous layer, becomes much thicker than the outer or pigmented layer (Fig. 175). The thickening does not, however, extend to the margin of the cup; a thinner

portion, the pars cæca, remains about the pupillary opening, separated from the thicker pars optica by a distinct offset, the ora serrata (Fig. 177). From the pars optica and the underlying pigment layer develops the retina; from the thin margin of the optic cup beyond the ora serrata develop the double epithelium covering the ciliary body and the posterior surface

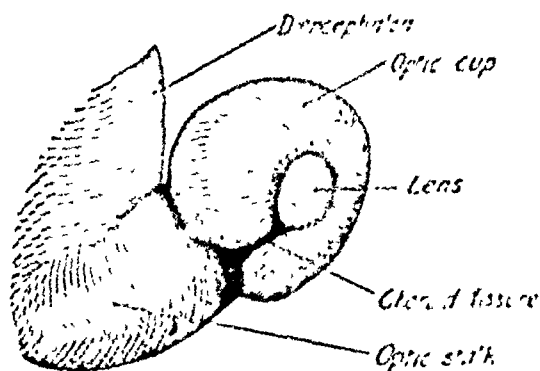


FIG. 176 Superficial view of optic cup and stalk with lens in place, as in human embryo 12.5 mm. long (about 6 weeks). (After Hochstetter in Kollmann's *Handatlas*.)

of the iris and the muscle fibers of the iris.

The pigment layer of the optic cup develops without much change into the pigment layer of the retina (Fig. 177). The inner or nervous layer of the cup develops into the nervous layer of the retina. Inasmuch as the optic cup is an outgrowth of the neural tube, the retina is in reality a part of the brain and develops in much the same manner. In its early development the nervous layer of the optic cup differentiates into two layers: (1) a zone containing many nuclei, corresponding to the ependymal and mantle layers of the neural tube, and (2) a fibrous layer without nuclei, corresponding to the marginal layer (Figs. 175 and 177). The marginal layer faces the cavity of the optic cup, a position corresponding to the outside of the neural tube.

The cells of the mantle layer give rise to both the supporting and the nervous cells of the retina. The nervous elements differentiate into two main types of cells: (1) the visual cells including the rod cells and the cone cells, and (2) the nerve cells, including chiefly the bipolar cells and the ganglion cells. The rod cells and the cone cells are intermingled in the deepest part of the nervous layer. The bipolar cells, which develop processes of no great length, occupy the middle zone. The ganglion cells in the superficial part of the mantle layer produce short dendrites extending downward toward the bipolar cells and long processes which grow upward into the marginal layer, where they become the axones of the nerve fiber layer of the retina.

The Optic Nerve. The axones of the nerve fiber layer converge toward the base of the optic cup, which they leave through the choroid

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The Mesodermal Parts of the Eyeball The optic cup and the lens vesicle are, from the first, surrounded by the loose mesenchyme of the

head (Fig. 175). From this tissue develop a number of important parts of the eyeball.

The Sclera and the Choroid. Soon the mesenchyme immediately surrounding the optic cup condenses into a denser capsule (Fig. 177).

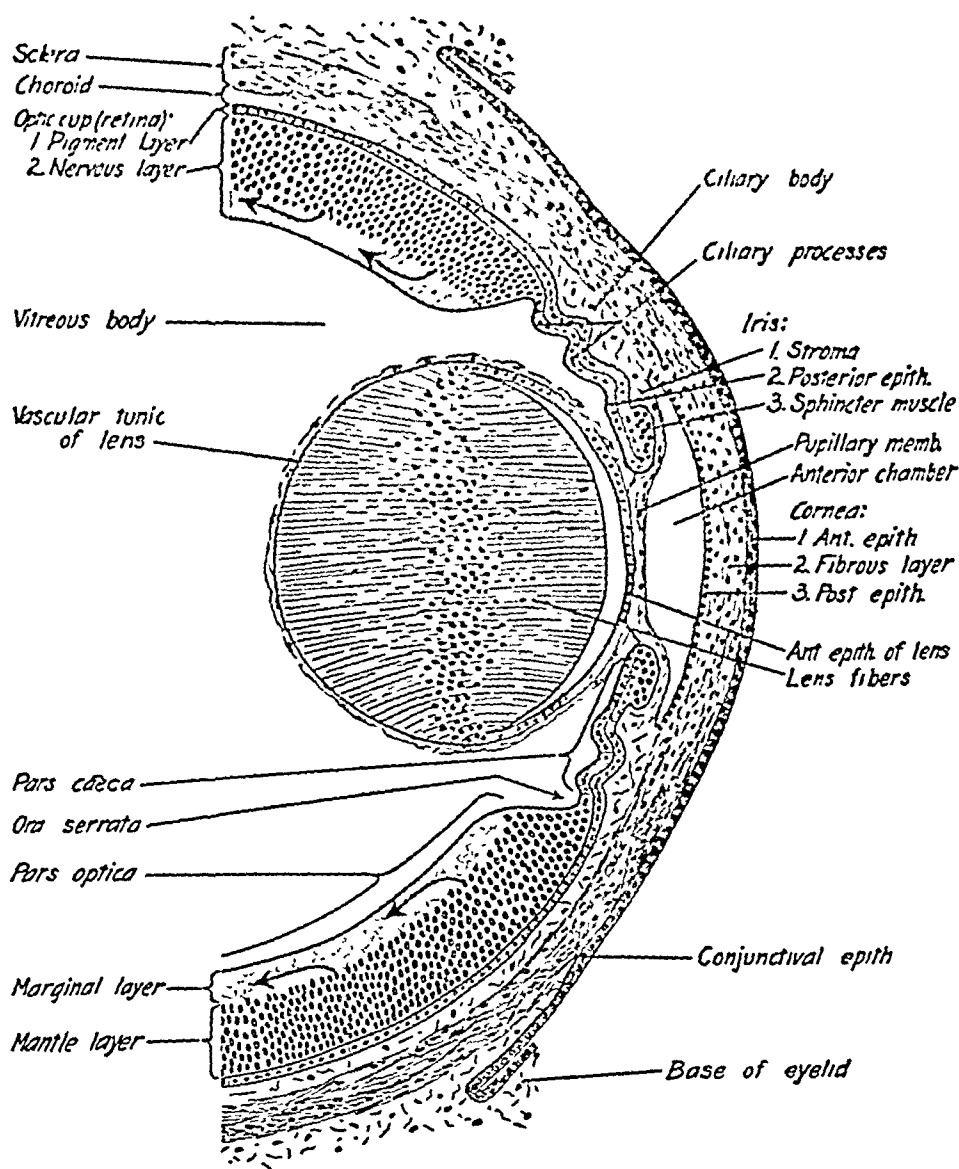


FIG. 177. Diagrammatic section through the front of an eyeball, as in a fetus about 4 months old. The arrows in the retinal part of the optic cup show the direction of growth of optic fibers from the ganglion cells in the retina toward the optic nerve.

Except in the region opposite the pupillary opening, the outer layer of this capsule develops into a very dense, opaque connective tissue, which forms the sclera. Between the sclera and the optic cup the con-

nective tissue is less dense, forming the choroid layer, which is continuous with the stroma of the ciliary body

The Cornea and the Anterior Chamber The mesenchyme opposite the pupillary opening (between the optic cup and the surface ectoderm of the head) is at first a continuous mass, but a cavity, the anterior chamber of the eye, soon develops in it. The anterior chamber separates this mesenchyme into two layers, an outer corneal layer, just beneath the ectoderm, and an inner layer covering the margin of the optic cup and closing the pupillary opening (Fig 177). From the corneal layer develop the dense but transparent fibrous layer of the cornea and the posterior epithelium (Fig 177). The ectoderm covering the corneal area becomes the stratified anterior epithelium of the cornea. It also extends over part of the sclera as the conjunctival epithelium.

From the inner layer develop the anterior epithelium and the stroma of the iris and the pupillary membrane, which temporarily closes the pupillary opening. The pupillary membrane is closely applied to the front surface of the lens vesicle as part of the fibrous, vascular tunic which furnishes the blood supply for the lens, inasmuch as the lens vesicle is devoid of blood vessels. It normally disappears shortly before birth, leaving the opening in the iris known as the pupil.

The Blood Vessels of the Eyeball The parts of the eyeball derived from mesenchyme develop their own blood vessels, as do other mesenchyme-derived structures, the internal parts derived from ectoderm require special notice. The lens vesicle early becomes surrounded by a vascular coat of mesenchyme, the vascular tunic of the lens (Fig 177). The entire vascular tunic normally disappears before birth. The permanent lens capsule is considered a product of the lens vesicle.

About the fifth week the hyaloid artery enters the optic cup through the choroid fissure at the attachment of the optic stalk. It sends large branches to the developing retina and also crosses through the vitreous body to the lens vesicle, where it ramifies in the vascular tunic to furnish the vascular supply for the developing lens. By the time of birth the hyaloid artery has degenerated, leaving in its place a more fluid part of the vitreous body known as the hyaloid canal. The part of the artery distributing to the optic cup persists as the central retinal artery.

ACCESSORY STRUCTURES OF THE EYE

The Eyelids The eyelids arise as folds of the skin just above and below the eye. These folds make their appearance in embryos about

seven weeks old. They grow broader until they cover the eyeball, and about the third month meet and fuse. The eyes remain closed until about the seventh month. The eyelids are thus essentially flaps of skin, which become specialized to include the various structures found in an eyelid. The ectoderm covering the face and giving rise to its epidermis is continued over the eyelids and around their edges to their under surface, where it forms the conjunctiva of the eyelids and then continues over the surface of the eyeball as the conjunctival epithelium of the sclera and cornea. The eyelashes develop as do other hairs. The tarsal glands arise as ectodermal ingrowths at the edge of the eyelids.

The Lachrymal Glands. The lachrymal glands arise as solid ingrowths of ectoderm into the subjacent mesoderm, along the line where the upper lid and eyeball meet.

The Naso-Lachrymal Duct. The naso-lachrymal duct develops in connection with the groove which in early embryos connects the eye and the olfactory pit (Figs. 28, 29, and 86, pp. 49 and 128). The epithelium at the bottom of this groove separates from the superficial part of the groove and sinks into the underlying mesoderm as a solid cord of ectodermal cells. A lumen later develops in it, producing a duct which connects the inner corner of the eye with the inferior meatus of the nose.

The Extrinsic Muscles of the Eye. The six muscles of the eyeball develop from mesenchyme adjacent to the eyeball, and, as previously indicated, they probably represent three myotomes of the head region.

E. THE EAR

The ear includes three parts: inner, middle, external. These parts develop from quite diverse sources, the nature of which would not be suspected from the structure of the adult ear.

The Inner Ear

General Structural Plan. The adult inner ear is composed of the bony labyrinth, a curiously shaped cavity in the temporal bone, and the membranous labyrinth within the bony labyrinth. The membranous labyrinth is essentially a fibrous bag lined with epithelium, in certain parts of which are the terminations of the auditory nerve. Within the membranous labyrinth is the endolymph space, and between the membranous and bony labyrinths is the perilymph space.

The epithelial lining of the membranous labyrinth is derived as follows from part of the ectoderm covering the head. In embryos of

about 2 mm (about four weeks) two thickenings of the ectoderm appear on the sides of the head opposite the middle of the myelencephalon. These are the auditory placodes. These areas soon become indented as the auditory pits (Fig 178A). These pits become deeper, developing into the two auditory or otic vesicles, which soon become

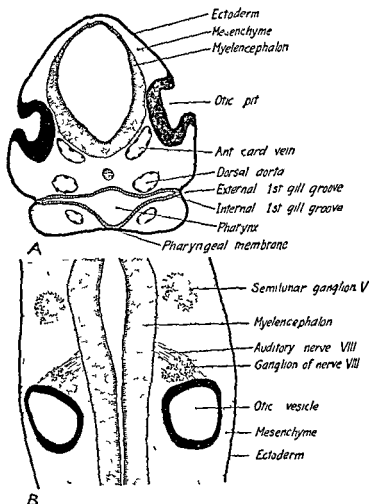


FIG 178 Early stages in the development of the inner ear of chick embryos A, transverse section through the head of a 48 hour chick, showing the auditory pits B frontal section through head of 72 hour chick, showing closed auditory vesicles and their relation to the developing auditory ganglion

separated from the ectoderm and lie freely in the mesenchyme of the head (Figs 22, p 45, and 178B). The auditory vesicles are at first approximately spherical, but become more and more elaborate in form until by the ninth week the cochlea, saccule, utricle, and semi-circular canals have taken form, as shown in Fig 179.

While the epithelium of the auditory vesicle is developing as just

described, the mesenchyme immediately surrounding it develops into a thin, fibrous basement membrane for this epithelium (Fig. 180). The basement membrane and the epithelium together form the membranous labyrinth.

At the same time the mesenchyme outside the membranous labyrinth develops into hyaline cartilage. In embryos of the second month the part of the cartilage immediately surrounding the basement membrane begins disintegration, which results in the formation of the

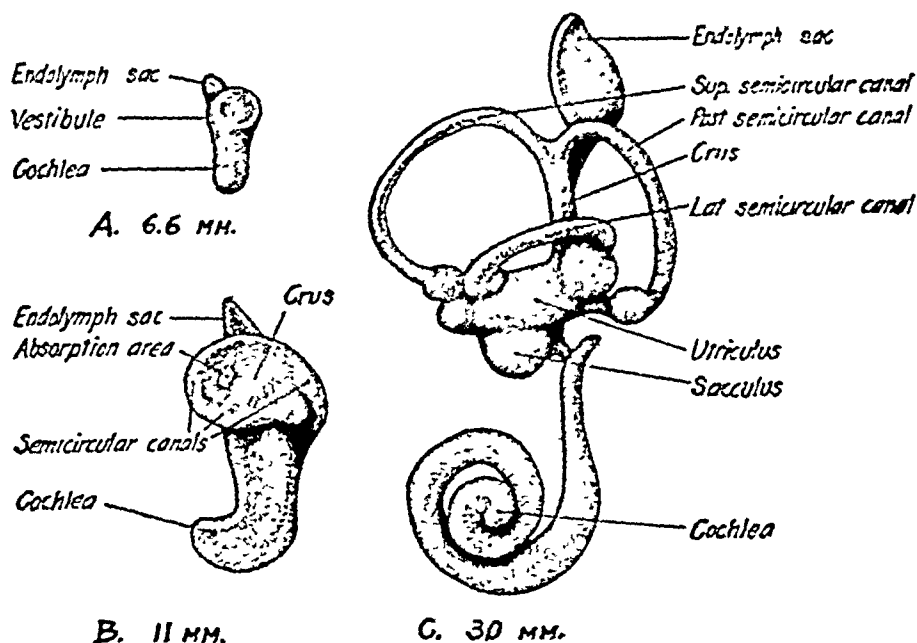


FIG. 179. Three stages in the development of the human membranous labyrinth. (Redrawn from Streeter in *Am. Jour. Anat.*)

perilymph space, a cavity permeated by a very loose fibrous tissue (Fig. 180). Ossification of the surrounding cartilage to form the petrous part of the temporal bone completes the development of the bony labyrinth. The inner ear has practically its adult size at birth.

Nerve Terminations. The cristae, the sensory areas in the ampullae of the semicircular canals, and the maculae in the saccule and utricle develop from local specializations of the ectodermal epithelium lining the membranous labyrinth, in relation to the terminations of the vestibular nerve. The epithelium in these areas differentiates into two types of cells, the sustentacular cells and the sensory (hair) cells. The branching ends of the nerve fibers come into intimate contact with the hair cells (compare taste buds, p. 259). The cupula of the crista and the otolith membrane of the macula are secretions of the epithelial cells.

The organ of Corti develops from a long band of epithelium in the cochlear duct. In general its cells develop as do those of other epithelial sensory endings, in that both sustentacular cells and hair cells are produced. The fibers of the cochlear nerve terminate in the hair cells. The development is complicated, however, by the fact that four kinds of sustentacular cells develop, namely, the border cells, the phalangeal cells, the pillar cells, and the cells of Hensen, as well as several other kinds of epithelial cells, all of which contribute to the complicated structure of the organ of Corti. The tectorial membrane develops as a gelatinous secretion of the epithelial cells. It ultimately becomes detached except at its connection with the limbus. A high differentiation of the basement membrane underneath the epithelium of the organ results in the formation of the auditory strings and the other specialized structures of this membrane.

The Middle Ear

In considering the development of the middle ear, it should be remembered that the otic vesicles from which the inner ear develops are formed in the sides of the head just above the dorsal side of the

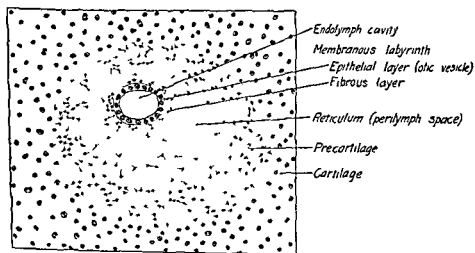


Fig 180 Section through semicircular canal of human fetus 46 mm long (about 10 weeks) Semidiagrammatic (Adapted from Streeter in *Cont to Emb*, Carnegie Inst, Washington)

first branchial grooves (Fig 22, p 45). The significance of this location is apparent when it is remembered that the middle and external ears are developed from the first branchial pouches and branchial grooves and portions of the first and second arches.

The Auditory Ossicles The three auditory ossicles develop from portions of the cartilages of the first and second branchial arches at

the dorsal ends of the arches (Figs. 64, p. 98, and 181). The malleus develops from the proximal end of Meckel's cartilage, the slender rod of cartilage in the mandibular process of the first arch, which forms the lower jaw in the elasmobranch fishes, such as sharks (Fig. 63, p. 97). The incus develops from the quadrate cartilage in the maxillary process. It is a small remnant of the large palatoquadrate cartilage, which forms the upper jaw in the elasmobranchs. The human incus and the malleus are the relics of the jaws in those fishes, the jaws in human beings and other mammals being more recent bones developed in membrane (p. 101). In this connection it should be remarked that in most textbooks of human embryology it is stated that the incus, as well as the malleus, develops in Meckel's cartilage, whereas other writers, chiefly in the field of comparative anatomy, describe its development as does this book. There is no recent, critical embryological study on this point, but it is of interest that in human embryos as small as 21 mm. in length the incus is already a separate cartilage, whereas the malleus is an unseparated part of Meckel's cartilage and remains so for some time (Figs. 64, p. 98, and 181).

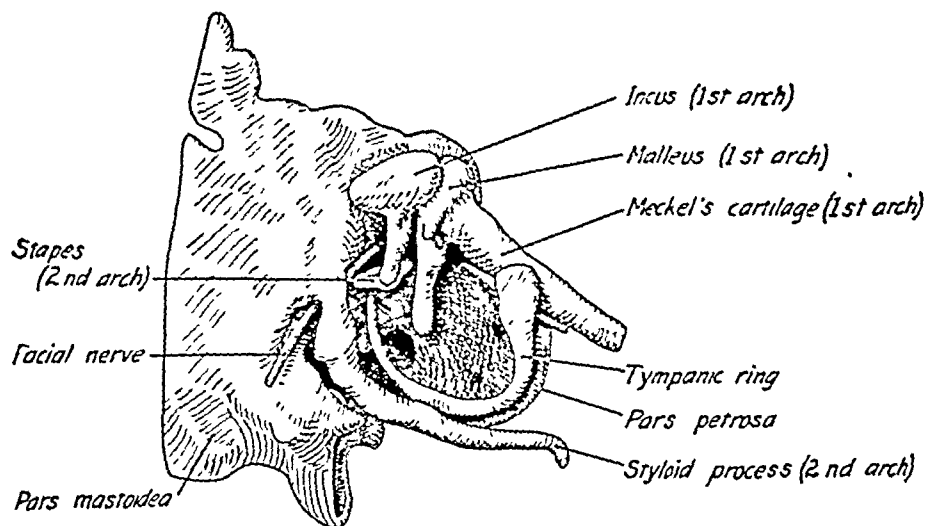


FIG. 181. The auditory ossicles of a human fetus 80 mm. long (about 13 weeks). (Redrawn from Kollmann's *Handatlas*.)

The stapes develops in the dorsal end of the cartilage of the second arch. The auditory ossicles begin to ossify during the fifth month and by the time of birth have attained their adult size. The tensor tympani muscle and its tendon develop from part of the mesenchyme of the first arch.

The Tympanic Cavity. The cavity of the middle ear (the tympanic cavity) and the Eustachian tube develop from the first branchial

pouch (Fig 178A) In the early human embryo the pouch is shallow and its lining entoderm comes close to the ectoderm of the external branchial groove, with only a little mesoderm between the two layers of epithelium As the embryo grows, the pouch becomes deeper At the same time its distal end expands to become a good-sized space, the tympanic cavity, and the three-layered membrane separating it from the external groove becomes the tympanic membrane The narrower part of the pouch becomes the Eustachian tube, which retains its primitive connection to the pharynx (Fig 182)

Until about the seventh month the auditory ossicles lie wholly outside the tympanic cavity in a position dorsal to it and between the external ear and the internal ear They are embedded in mesenchyme just as other bones are surrounded by soft tissues (Fig 182) Between

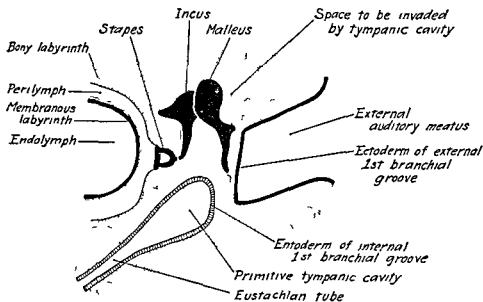


FIG 182 Diagram of the middle ear as in fetus about 7 months old, showing the auditory ossicles embedded in mesenchyme which will later degenerate to allow expansion of the tympanic cavity into the region surrounding the ossicles

the seventh month and birth the expansion of the tympanic cavity is rapid, and in this process the mesenchyme surrounding the auditory ossicles degenerates At the same time the entodermal epithelium lining the cavity expands to line the new part of the cavity, to cover the inner surface of the tympanic membrane, and also to envelop the auditory ossicles, as the peritoneum covers the abdominal organs Thus these bones lie within the tympanic cavity only in the same sense that the abdominal viscera lie within the abdominal cavity (Fig 182) The mastoid cells are not present at birth, but during the years of childhood they gradually form by expansions of the tympanic

cavity into the temporal bone. They too are lined with entodermal epithelium directly continuous with the mucous membrane of the nasal pharynx through the tympanic cavity and the Eustachian tube.

The External Ear

The external auditory canal is the persistent first branchial groove (Fig. 178A) and is consequently lined with an ectodermal epithelium, a direct continuation of the epidermis. The tympanic membrane is also covered on its outer surface with epithelium from the same source, underneath which is its connective tissue layer which develops from

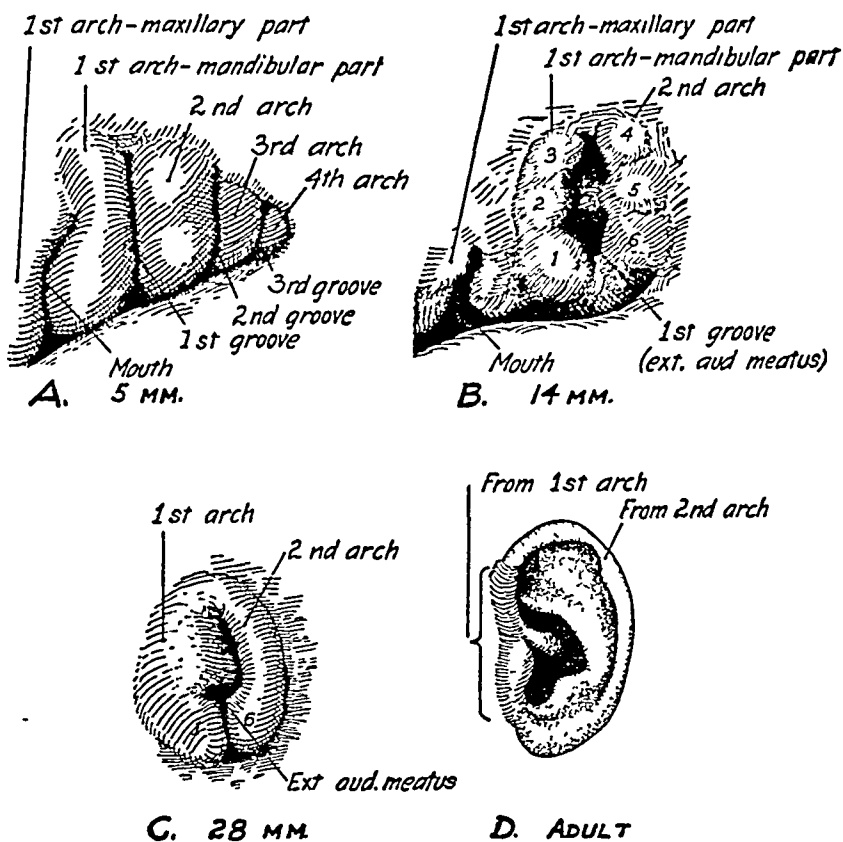


FIG. 183. Four stages in the development of the human external ear. A, side view of pharyngeal region of human embryo 5 mm. long (5 weeks). B, from embryo 14 mm. long (6½ weeks), showing the six elevations on the edges of the first branchial groove. C, external ear of a fetus 28 mm. long (about 8½ weeks). D, the adult human ear. The parts derived from the first and second arches are shaded differently. (Redrawn from Streeter in *Cont. to Emb.*, Carnegie Inst., Washington.)

mesenchyme (Fig. 182). The development of its inner epithelium from the entodermal lining of the tympanic cavity has already been described.

The auricles develop from parts of the first and second arches bounding the first branchial grooves (Figs 27 to 30, pp 48 to 50) Figure 183 illustrates the development of the auricle as viewed from the side, beginning with an embryo of 5 mm (five weeks) and tracing it to the adult condition From these drawings it will be seen that during the seventh week three swellings appear on each side of the groove These swellings soon merge into a ridge in which the form of the adult ear gradually develops It will be seen that the second arch contributes more to the adult ear than does the first

F ANOMALIES

The Eye The choroid fissure sometimes fails to close perfectly, leaving a defect in the iris, ciliary body, and choroid, known as coloboma. The pupillary membrane sometimes persists in whole or in part as an opaque closure of the pupil Pigmentation is sometimes wholly wanting from the eye, a condition usually associated with general albinism Cyclopia is produced by the fusion of the two eyes to form one eye in a median position Hare lip, cleft palate, and other facial defects are often associated with this condition

The Ear The external auditory canal is sometimes closed because of abnormal development in the region of the first external groove In non-development of the lower jaw the two external ears are united together in the mid-ventral line

CHAPTER XX

GENERAL NOTES ON DEVELOPMENT

In this chapter are presented summarized statements about certain important features of development, with the hope that they may prove useful as a general review of the matter included in the preceding chapters.

A. THE DERIVATIVES OF THE THREE GERM LAYERS

The reader is by this time familiar with the part played by each of the germ layers in the general plan of development, and it must now be quite apparent that the establishment of the germ layers marks an important step in cell specialization and lays the foundation for the formation of the organs. It is of considerable interest that these same three germ layers occur in the development of all vertebrates and most invertebrates, and that from each of them there develop in all these animals essentially the same adult structures as in human development.

Each germ layer at its beginning is already a specialized group of cells which has the capability of giving rise to only certain of the structures of the body. Further specialization within each germ layer and inter-relations between the layers gradually produce the complicated structures of the adult body. The general importance of each layer may be summarized as follows:

Ectoderm. Ectoderm, situated as it is on the outside of the embryonic body, develops largely into structures concerned with protection and the reception of stimuli from without. It is not surprising, therefore, that in all groups of animals it should give rise to the outer layer of the skin and to the nervous system and sense organs. Ectoderm produces, in the main, two tissues: nervous tissue and epithelium. The epithelium is of three sorts: protective, glandular, and sensory.

Entoderm. Entoderm lines the alimentary canal of the developing body and is concerned primarily with nutrition. From entoderm originate all the organs of digestion and respiration, as well as certain other structures which arise as outgrowths from the primitive gut. Entoderm produces epithelium only, and this epithelium is mostly of a secreting (glandular) and absorbing nature.

TABLE 7

ECTODERMAL DERIVATIVES

<i>Embryonic Structures</i>	<i>Adult Derivatives</i>
General surface of body	Epidermis, hairs, nails Sudoriferous glands, sebaceous glands, mammary glands Conjunctival epithelium Glands of the eye
Oral pit	Epithelium of mouth and part of nasal cavities Small glands of oral and part of nasal cavities Salivary glands Anterior lobe of hypophysis Enamel of teeth
Olfactory pits	Epithelium and glands of part of nasal cavities
Anal pit	Epithelium of anal canal
Lens vesicle	Crystalline lens
Otic vesicle	Epithelium of membranous labyrinth including sensory epithelium of ear
Neural tube and neural crest	Brain and spinal cord Cranial, spinal, and autonomic ganglia Cranial, spinal, and visceral nerves Retina, posterior epithelium of iris and ciliary body Medulla of suprarenal gland Posterior lobe of hypophysis Pineal body

TABLE 8

ENTODERMAL DERIVATIVES

<i>Embryonic Structures</i>	<i>Adult Derivatives</i> (the Epithelium of the Parts Listed Below)
Pharynx	Oral pharynx, nasal pharynx Tympanic cavity, Eustachian tube Thyroid parathyroids, thymus Taste buds Larynx
Esophagus	Esophagus Trachea, bronchi, lungs
Stomach	Stomach
Intestine	Small intestine, cæcum appendix large intestine Liver, pancreas
Cloaca 1 Rectum	Rectum
2 Urogenital division	Urinary bladder urethra, vaginal vestibule Prostate gland paraurethral glands Bulbourethral glands vestibular glands

Mesoderm. Mesoderm gives rise to a great variety of tissues and produces far more of the mass of the body than both the other layers together. Not only is mesoderm the great source of supporting, muscular, and vascular tissues, but it also produces much epithelium and some sensory structures. Mesoderm contributes largely to all the organs which have their origin in ectoderm and entoderm.

TABLE 9

MESODERMAL DERIVATIVES

<i>Embryonic Structures</i>	<i>Adult Derivatives</i>
Notochord	Pulpy nuclei of intervertebral discs
Somites: 1. Dermatome } 2. Myotome } 3. Sclerotome	Muscles of trunk Vertebrae, ribs
Intermediate cell mass (nephrotome)	Pronephros (embryonic) Mesonephros (mostly embryonic) Kidney, ureter Epididymis, sperm duct
Lateral plate:	Pleural membranes, pericardial membrane, peritoneum Ovary, testis Fallopian tubes, uterus, vagina
1. Somatic layer	Dermis, superficial and deep fascia Sternum, skeleton of limbs Muscles of limbs Cortex of suprarenal gland
2. Splanchnic layer	Muscles and connective tissue of alimentary canal Cartilage, connective tissue, and muscles of larynx, trachea, and lungs Fibrous parts of liver, pancreas, prostate, and other glands Muscles and connective tissue of urinary bladder and urethra Organs of circulation, blood, lymph. These organs have their origin in splanchnic mesoderm, whence they spread to all parts of body. They retain their splanchnic nerve supply.
Mesoderm of head:	
1. Pharyngeal part	Bones of jaw, dentine, cement Auditory ossicles, hyoid bone Muscles of mastication, expression, etc.
2. General mesenchyme of head	Bones developed from chondrocranium Membrane bones (except jaws) Eyeball (except ectodermal parts) Inner ear (except ectodermal parts)

Tables 7, 8, and 9 express in compact form the main embryonic divisions of each germ layer and its adult derivatives. For mesoderm an exact classification is, in some respects, difficult, because mesenchyme is so widely spread in the embryonic body that it is occasionally somewhat uncertain just what is the source of the mesenchyme of a given organ.

B THE ADULT DERIVATIVES OF THE PHARYNX

In previous chapters it has been seen that the pharynx plays an important part in the development of several systems of organs. It may now be of interest to summarize the development of this small but important region of the body. The embryonic pharynx in human development corresponds structurally to the pharynx of adult fishes, which is respiratory in function. In the arches of the embryonic human pharynx there form cartilages, muscles, and blood vessels corresponding to those found in the pharynx of fishes, and to each arch large branches grow from certain of the cranial nerves, also agreeing with those of fishes. This phase of the human pharynx is only temporary, the region soon undergoing a remarkable transformation and giving rise to structures which bear no resemblance to those of the embryonic pharynx. The results of this transformation are expressed in Table 10.

C SCHEDULE OF DEVELOPMENT

While one is studying the development of the systems of organs one by one, he may fail to realize fully that all the organs of the body are developing at the same time. From the preceding chapters no adequate conception of the embryo as a whole nor of the sequence of the various events of development is obtained. For this reason it may be helpful to add a brief outline of the main events of development arranged by weeks and months.

First Week Begins with ovulation. No observations on human ova. Cleavage and formation of blastocyst, trophoderm, and inner cell mass. Implantation begins late in the week (Figs 10 and 11, pp 31 and 32.)

Second Week Implantation completed about eleventh day. Trophoderm becomes a spongy mass containing some maternal blood. Amniotic cavity, primitive yolk sac, and extra-embryonic mesoderm form. Extra-embryonic coelom appears. Youngest known human embryos fourteen days, Peters (1899), twelve to thirteen days, Bryce and Teacher (1908), eleven days, Miller (1913), nine to ten days, Hertig

TABLE 10

THE ADULT DERIVATIVES OF THE PHARYNX

Parts of Pharynx	Nerve Supply	Adult Derivatives				
		Skeleton	Muscles	Arteries	Glands	Miscellaneous
1st arch	Trigeminal	Maxilla Palatine Mandible Incus Malleus	Mastication			Tongue (pt) External ear (pt)
1st groove						External auditory meatus
1st pouch					Thyroid from floor of pharynx (not from pouch)	Tympanic cavity Eustachian tube Tongue (pt) from floor of pharynx
2nd arch	Facial	Styloid process Stapes Hyoid (pt)	Expression			Tongue (pt) External ear (pt)
2nd pouch						(Tonsils)
3rd arch	Glosso-pharyngeal	Hyoid (pt)	Pharynx (pt)	Internal carotid		Epiglottis (pt)
3rd pouch					Para-thyroid III	Thymus III
4th arch	Vagus and accessory (pt)	Thyroid cartilage (pt)	Pharynx (pt) Larynx (pt)	Arch of aorta R. sub-clavian		Epiglottis (pt)
4th pouch					Parathyroid IV Ultimo-branchial bodies	Thymus IV (rare)
5th arch	Vagus and accessory (pt)	Thyroid cartilage (pt)	Pharynx (pt) Larynx (pt)			
5th pouch	Very rare					
6th arch				Pulmonary Ductus arteriosus		

and Rock (1942), seven to eight days, Hertig and Rock (1942) (Figs 11 to 15, pp 32 to 38)

Third Week Trophoderm develops into chorion with branched villi. Body stalk and allantois form. Embryonic disc forms and late in week the embryo begins to develop, with head fold and fore gut, primitive streak, embryonic mesoderm, notochord, neural groove, and neurenteric canal. Blood vessels and blood form in extra-embryonic regions (Figs 15, 16, and 18, pp 38, 41, and 42)

Fourth Week Embryo forms definitely and at end of week has length of 2.5 mm. Head and tail folded off from yolk sac, but yolk stalk is still very broad at the end of the week (Figs 19 and 20, p 43)

The following important structural advances take place. Neural tube begins to close, but is still open in brain region at end of week. Primitive streak disappears. Pharynx enlarges. Embryonic type of circulation established. Epidermis becomes two-layered. The following make their first appearance: heart tube, first somites, first branchial grooves, tuberculum impar (first rudiment of tongue), liver bud (2.5 mm), laryngo-tracheal groove (2.5 mm), septum transversum (2-3 mm), pronephros (1.7 mm)

Fifth Week CR length 2.5-5.5 mm. Form of body becomes typically embryonic. Flexures begin to form. Lamb buds appear. Yolk stalk becomes narrow (Figs 21 and 22, pp 44 and 45)

Pharyngeal membrane ruptures (3 mm). Stomach begins to enlarge and to rotate (4-5 mm). Pronephros disappears (4.25 mm). Pronephric duct reaches cloaca (4.2 mm). Neural tube closes. Optic vesicles appear (2.5 mm) and become cup-shaped (4.9 mm). The following make their first appearance: olfactory pits (4 mm), anterior lobe of hypophysis (Rathke's pouch) (3 mm), thyroid rudiment (3 mm), pancreas buds (3-6 mm), mesonephros (2.5 mm), metanephric bud (5 mm), genital ridge (5 mm), three primary brain vesicles (2.5 mm), cerebral hemispheres (late), lens vesicle (4 mm), auditory pits (2.6 mm)

Sixth Week CR length 5.5-11 mm. Flexures become pronounced. Brain becomes large and determines shape of head. Branchial arches and grooves are very prominent but begin to disappear toward close of week. Hand becomes paddle-shaped. Heart very prominent externally. Eye apparent externally. Yolk stalk closes (9 mm). Umbilical cord forms (Figs 23 and 24, p 46)

Full number of somites attained. Muscles of trunk still show segmentation. Thyro-glossal duct breaks. Large intestine begins to expand (7 mm). Pleuro-pericardial membranes complete (11 mm)

Mesonephros at greatest development. Migration of neuroblasts to autonomic ganglia. The following make their first appearance: thymus (6 mm.), spleen (9 mm.), nephrogenic cap of metanephros (7 mm.), Müllerian duct (10 mm.), genital tubercle (early), five divisions of brain, fetal suprarenal cortex (7-8 mm.).

Seventh and Eighth Weeks. CR length 11-25 mm. Form gradually changes from embryonic to fetal. Flexures largely obliterated. Neck forms and head becomes erect. Branchial arches and grooves disappear. Face forms. Eyes become prominent and lids begin to form. Joints and digits form in limbs. Tail becomes overgrown. Heart less prominent externally. Ventral contour of body becomes rounded because of gut, liver, and heart. (Figs. 25 and 26, p. 47.)

Cartilages present for nearly all bones (seventh week). Branchial cartilages well formed (21 mm.). Many primary centers of ossification formed, including some in membrane bones of skull. Nearly all skeletal muscles may be recognized (20 mm.). Coils of intestine enter umbilical cord (19 mm.). Cloaca divides into rectum and urogenital part (15 mm.). Dorsal and ventral pancreas buds unite (20 mm.). Pleural sacs enclosed by development of pleuro-peritoneal membranes and completion of diaphragm (19 mm.). Recession of diaphragm complete (24 mm.). Transformation from embryonic to fetal circulation complete at end of eighth week. Mesonephros, except for twenty-six tubules, degenerates (21 mm.). Genital ridge of male begins sexual differentiation (13 mm.). Müllerian ducts reach urogenital sinus (24 mm.) and begin to unite, forming utero-vaginal canal (24 mm.). Urethral membrane ruptures (17 mm.). Male urethral groove begins to close, forming penile part of urethra. All main features of autonomic system outlined (16 mm.). The following make their first appearance: sublingual gland (24 mm.), jugular lymph sacs (18 mm.), posterior and retroperitoneal sacs and cisterna chyli (23 mm.), first renal corpuscles, dorsal and ventral gray columns of spinal cord, permanent suprarenal cortex (11-13 mm.), chromaffine cells of suprarenal medulla (13-14 mm.), union of suprarenal cortex and medulla (19 mm.).

Third Month. CR length 25-68 mm. Head still very large. Eyelids close and fuse. Nail rudiments appear. First hair buds form. Sex may be distinguished externally.

Rotation of stomach complete. Intestine withdrawn from umbilical cord (40 mm.). Anal membrane ruptures (30 mm.). Liver at maximum relative size (10 per cent of body). Kidney becomes lobulated. Genital ridge of female begins sexual differentiation. Mesonephric duct begins degeneration in female and Müllerian duct in male (ninth week). Male

urethra closes to tip of penis Palate complete to posterior margin but nasal septum not yet completely fused to palate The following make their first appearance enamel organs, lymph nodes, urogenital union in both sexes (ten weeks), prostate, bulbourethral, vestibular, and paraurethral glands

Fourth Month CR length 68-121 mm Epidermis becomes many-layered Skin transparent and bright red because blood shows through Lanugo appears Muscles become active and fetal movements are sometimes felt by mother Fetal heart beats sometimes audible Enamel organs for some of the permanent teeth form Tonsils begin to form Medullation of nerve fibers begins Suprarenal glands larger than kidneys

Fifth Month CR length 121-167 mm Nails can be distinguished Body lean Skin less red Sudoriferous glands begin to form Enamel and dentine begin to form

Sixth Month CR length 167-210 mm Body still lean Eyelids separate Lashes and eyebrows form Epitrychium shed and vernix caseosa begins to form Convolutions begin to form on cerebral hemispheres

Seventh Month CR length 210-245 mm Fetus looks like little, wrinkled, old person with red skin Eyelids open Testes sometimes enter scrotum Child may sometimes be kept alive if born

Eighth Month CR length 245-284 mm Skin still red but less wrinkled and child less lean Testes usually enter scrotum May generally be reared with great care

Ninth Month CR length 284-316 mm Lanugo begins to shed Redness fades and wrinkles begin to smooth out Nails at tips of fingers Child more easily reared but still requires unusual care

Tenth Month CR length 316-336 mm Skin white to pinkish Nails beyond ends of fingers

D GENERAL NOTES ON ANOMALIES

In the great majority of cases the egg undergoes what may be called a normal development, the external form and the various internal organs developing in an orderly manner quite similar to the development of other individuals Sometimes, however, the development departs in varying degrees from the normal Such departures are known as anomalies If the anomaly is slight, it in no way impairs the health of the individual, and he may live to a good old age If it is extremely serious, it causes the death of the embryo at a very early age Many other anomalies of varying degrees of seriousness range

between these extremes. If an anomaly is of such a nature as to greatly distort the external form, it is known as a **monstrosity**.

Kinds of Anomalies. Anomalies are of two general sorts: (a) those which involve only one individual, and (b) those which involve more than one individual (usually two), resulting in the production of identical twins and the various kinds of double monsters. The latter type was treated in Chapter V on the external form, and various kinds involving only one individual have been mentioned in the several chapters treating the systems of organs.

Congenital anomalies involving one individual include many kinds of structural defects, which owe their origin in the main to the following abnormal developmental processes:

1. *Failure of rudiments to appear* at all or to develop into organs of the usual size (for example, absence or small size of eyes, limbs, or various viscera).

2. *Unusual multiplication of rudiments* to produce supernumerary organs (for example, supernumerary digits, ribs, vertebrae, and various internal organs)

3. *Failure of rudiments to fuse*, resulting either in malformed structures or multiple parts (for example, hare lip, cleft palate, hernia, double uterus and vagina).

4. *Abnormal fusions* (for example, closure of lumen of various viscera, fusions of legs and digits, and fusion of eyes in cyclopia).

5. *Failure of embryonic structures to degenerate* (for example, cysts from branchial grooves and the thyro-glossal duct, Meckel's diverticulum, various forms of spurious hermaphroditism, supernumerary mammary glands, persistent tail, double aorta).

6. *Abnormal attitudes or positions* of organs (for example, partial or complete transposition of viscera, non-descent of testes, descent of kidneys).

Teratomata. A very interesting and important group of anomalies of development includes the structures known as teratomata. These anomalies do not fall within any of the six types listed but are more closely related to double monsters. A teratoma is a tumor-like growth consisting of tissues which do not belong at the part of the body where the tumor occurs. Such growths are to be regarded as congenital, though few of them are recognized as early as the time of birth, and some do not develop until late in life. Teratomata include solid tumors and hollow growths or cysts. Any or all of the germ layers may be involved in their formation.

Familiar examples are various ectodermal cysts lined with stratified squamous epithelium either with or without hairs and skin glands,

such as the cysts which form in the neck region from enclosed remnants of the external branchial grooves. The internal branchial grooves, in a similar manner, sometimes give rise to entodermal cysts. Similar cysts are also formed at the base of the tongue from unde-generated remnants of the thyro-glossal duct. In the broad ligament and uterine tubes cysts form from remnants of the Wolffian ducts. Portions of suprarenal gland are sometimes found in the kidneys, liver, and other organs. In a similar manner cartilage may be developed in, for example, the salivary glands, mammary glands, skin, and testes, and striated skeletal muscle in such parts as the kidneys, testes, heart, and uterus. These are but a few examples of the many which might be given. In all cases the explanation is that a rudiment has become misplaced and instead of degenerating has undergone growth in the unusual location.

There are also teratoid cysts and tumors of more complicated structure, including material from all the germ layers, often organized into organs. The most abundant of such growths are teratoid ovarian tumors and cysts which may include skin, hairs, teeth, bones, nervous tissue, eyes, glands, tracheal and lung tissues, and intestinal villi. Such growths are also found, though less frequently, in the testes and some other parts of the body. They may form at any age but are more common in childhood and early adult life in contradistinction to ordinary tumors and cancers, which develop more frequently after middle life. Some of them attain considerable size and some become malignant.

Such tumors have been explained in various ways, but the most widely accepted view is that they represent the body of a conjoined twin the development of which has been delayed. They are thus related to double monsters and identical twins, in fact, there are all intermediate conditions connecting the two extremes. The same underlying cause in all probability is therefore responsible for the production of identical twins and double monsters of both equal size and unequal size. Teratoid tumors are but an extreme instance of unequal twins in which the development of one twin was inhibited at the normal time, only to take place at a later time, giving rise to a parasite within its host twin.

Time of Origin of Anomalies. By their very nature anomalies must have their origin extremely early in prenatal life, that is, in the main during the embryonic period while so many organs are in the process of development, or while the embryonic organs are undergoing transformation into the fetal organs. The schedule of development on pp 277 to 281 shows clearly the rapidity with which organs are forming

during the second and third months. Once the fetal body has attained its internal organization and external form, little opportunity is left for the initiation of new anomalies, though those which have originated earlier persist. The early origin of anomalies is clearly shown by the large number of monsters among embryos which are aborted during the second and third months.

There is a striking correlation between anomalies and abortion in the fact that only about one-twelfth of all anomalous embryos live to full term. By far the greater number die and come to premature birth before the sixth month, about 60 per cent during the second and third months. Anomalous embryos comprise about one-third of all premature births, but only about three-fourths of 1 per cent of those which come to full term have apparent anomalies. The anomalies are frequently the obvious cause of the death of the embryo. A dead embryo is, as a rule, soon expelled from the uterus. Anomalous development is therefore a very important cause of premature births.

Frequency of Anomalies. It is by no means easy to gather accurate statistics concerning the frequency of anomalous development, but the figures of Mall, based on an estimate from his own observations and those of other students of the subject, indicate that about 7 per cent of all pregnancies result in anomalous development, though only three-fourths of 1 per cent of all pregnancies result in full-term anomalous infants. It also is of interest that about 20 per cent of all pregnancies fail to come to full term.

Of those anomalous infants which come to birth at full term, a very few, on account of the nature and extent of their structural defects, die very shortly. By far the greater number, however, continue to live, some with external disfigurement and others with internal defects which lead to ill health. Many other structural anomalies cause no evident impairment of function and remain unsuspected unless discovered during operations or autopsies.

Those monsters which die before birth are usually of a far more extreme type. Many of them are undersized and variously distorted both externally and internally. Others are but variously shaped assemblages of poorly organized tissues, whereas yet others are reduced to small nodular masses. Still more extreme are the cases in which the chorionic vesicle contains no sign of an embryo at all; in these cases the amnion may or may not be present. In the production of these extreme types, postmortem degeneration doubtless plays a part, so that it is impossible to be sure of the nature and extent of the initial defects, but often they are apparently very great.

The Causes of Anomalies Careful investigations into the causes of anomalies have seemingly shed light upon a question which has for centuries excited speculation. Until recent years the most commonly accepted explanation, except in the strictest scientific circles, has been that of *maternal impressions*. It was commonly believed that the mental state of the mother during pregnancy had a specific effect upon the body and the mind of the unborn child. Birthmarks and monstrosities were commonly explained in this way, even by many obstetricians. This view, however, has now largely been abandoned by well-informed people, on account of lack of reasonable evidence in its favor.

Though the exact cause of a given anomaly can seldom, if ever, be determined, there are, in general, two possible underlying causes: (1) the *inheritance* of defects through the egg or sperm, and (2) the *effect of external influence* upon the developing individual.

That inheritance sometimes is a factor in anomalies is indicated by the fact that definite kinds of malformations are known to run in certain families, some of them being inherited in Mendelian fashion. Moreover, there seems every reason to believe that anomalies may be inherited just as may any normal structural peculiarity, so long as the anomaly is not serious enough to be self-eliminating. Not many anomalies, however, seem to be of the hereditary type.

On the other hand, it would be unreasonable to assume that external influence brought to bear upon the fertilized egg during its development may not have something to do with the production of anomalies, in fact, there is good reason to believe that many anomalies are so produced. This view has received its strongest support from experimental work upon the embryos of fishes, the results of which, when coupled with observations upon anomalous human embryos, have added much to the general understanding of the question.

The experiments on fish embryos demonstrated that anomalies may be produced by adding certain chemicals to the water in which these embryos are developing. Moreover, it was discovered that anomalies of specific kinds may be produced at will if development is interrupted at appropriate times by cooling the embryos to a critical temperature for a suitable period or by temporarily depriving them of adequate oxygen. Experiments of this type have shown that the type of malformation depends on the time at which the cause is operative. By selecting proper times, it is possible to produce desired degrees of twinning, ranging from double-headed or double-tailed monsters to completely double embryos. In the same way cyclopia

and various other defects of the eyes, including complete absence, may be produced, as may also malformed brains, deformed pharynx, short bodies, stunting or absence of inner ear, and inhibition of liver and pancreas.

The mode of operation of the method is explained thus: The rudiments of various organs begin growth at successive times in a definite sequence (not all at once). If a rudiment is inhibited from development at the normal time it may not be able to grow at all; for example, the eye is not only derived from a definitely localized group of cells, but it must also begin its development during a definite, limited time. Arrest of development is accordingly effective upon those organs which are in the critical stage during its operation.

In applying these principles to mammalian development it is widely believed that the great majority of mammalian monsters are very probably due to an insufficient oxygen supply during development, and that this condition, as a rule, is due to faulty placentation. Careful students of human anomalies are inclined to accept this explanation. Even before the experimental work on fish embryos, some authorities had come to believe that human monsters may result from faulty nutrition, which causes slowing of development and consequent arrest of certain rudiments. Delayed or faulty implantation is considered to be a possible cause of retarded development, which results in the production of identical twins and duplicate monsters of various sorts, as well as other kinds of anomalies. The prevalence of uterine diseases in connection with human monsters is worthy of consideration, as well as the frequency of defective development of the chorion. It is also significant that anomalous development has a far greater proportional frequency in tubal pregnancies than in normal uterine implantation, the obvious explanation being retarded development due to insufficient oxygen in the unfavorable tubal position, with consequent inhibition of certain rudiments.

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and various other defects of the eyes, including complete absence, may be produced, as may also malformed brains, deformed pharynx, short bodies, stunting or absence of inner ear, and inhibition of liver and pancreas.

The mode of operation of the method is explained thus: The rudiments of various organs begin growth at successive times in a definite sequence (not all at once). If a rudiment is inhibited from development at the normal time it may not be able to grow at all; for example, the eye is not only derived from a definitely localized group of cells, but it must also begin its development during a definite, limited time. Arrest of development is accordingly effective upon those organs which are in the critical stage during its operation.

In applying these principles to mammalian development it is widely believed that the great majority of mammalian monsters are very probably due to an insufficient oxygen supply during development, and that this condition, as a rule, is due to faulty placentation. Careful students of human anomalies are inclined to accept this explanation. Even before the experimental work on fish embryos, some authorities had come to believe that human monsters may result from faulty nutrition, which causes slowing of development and consequent arrest of certain rudiments. Delayed or faulty implantation is considered to be a possible cause of retarded development, which results in the production of identical twins and duplicate monsters of various sorts, as well as other kinds of anomalies. The prevalence of uterine diseases in connection with human monsters is worthy of consideration, as well as the frequency of defective development of the chorion. It is also significant that anomalous development has a far greater proportional frequency in tubal pregnancies than in normal uterine implantation, the obvious explanation being retarded development due to insufficient oxygen in the unfavorable tubal position, with consequent inhibition of certain rudiments.

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